UNIVERSITEIT GENT

FACULTY OF MEDICINE AND HEALTH SCIENCES

EVIDENCE-BASED PREVENTION OF HEALTHCARE-ASSOCIATED INFECTION

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SUMMARY

Healthcare workers' adherence to evidence-based guidelines for the prevention of healthcare-associated infections is reported to be restricted. Numerous barriers to guideline compliance have been self-reported. A lack of knowledge of the guidelines' contents has nevertheless not been included in the extensive list of self-reported hindrances to adherence. The goal of the EVIDENCE-project was to determine the level of knowledge about evidence-based guidelines for the prevention of healthcare-associated infection among healthcare workers, and to help enhancing awareness if deficiencies would be detected.

As a first step towards identifying potential gaps in healthcare workers' knowledge about this important topic, a needs analysis was conducted. Thereto, multiple choice questionnaires concerning the prevention of ventilator-associated pneumonia, central venous catheter-related infection and surgical site infection were developed. The reliability of these questionnaires was tested by means of item analysis and their contents were submitted to a panel of experts in order to obtain content validity. Subsequently, they were used to conduct surveys among intensive care nurses. The results of these surveys, of which two were conducted on a European scale, revealed overall disappointing scores below the conventional 50% threshold to pass a test.

In order to meet the needs detected, e-learning was chosen as an educational tool as it allows adult distant learners to study at times and places according to their own preferences, and at their own pace. Using open source software, a comprehensible Web-based *Crash Course* bundling the essentials on the prevention of healthcare-associated infections was developed. Various exercises allowing learners to self-evaluate their study progress were integrated. In order to facilitate access to the course worldwide, the only requirements for access are a computer with internet browser; no additional plug-ins or downloads are required. The course's contents were validated by a team of experts in the field of infection prevention, and its usability was tested and approved by means of the Software Usability Measurement Inventory (SUMI®).

To assess whether the course succeeds in increasing and sustaining knowledge among learners, a study website was created where all voluntary learners involved with patient care

could enroll. After submission of a pre-test, they were granted access to the course for a maximal period of eight weeks, which was followed by a first post-test to assess the immediate learning effect of the course. Actual study time was automatically logged. During the twelve weeks following this post-test, access to the course was denied. Subsequently, participants were invited to take a second post-test in order to measure their level of knowledge retention.

We found that limited time invested in studying the EVIDENCE *Crash Course* yielded significant increases in immediate (+24%) and residual (+18%) learning effects among nurses, physicians, students and allied healthcare professionals. Although the course was originally developed for ICU clinicians, healthcare professionals working outside the ICU also showed significant benefit from studying the course.

Additional research comparing different Web-based interventions is needed to elucidate how to implement e-learning most effectively. In the meantime, the results of the EVIDENCE-project strongly suggests that moderate time invested in a low-cost e-course with good usability features and exercises for self-evaluation can significantly enhance knowledge about the prevention of healthcare-associated infection.

SAMENVATTING

Talrijke publicaties rapporteren dat zorgverleners evidence-based richtlijnen voor de preventie van zorginfecties slechts in beperkte mate navolgen. Op basis van onderzoeksresultaten met een zelf-rapporteringsdesign werden reeds talrijke hinderpalen voor compliantie gerapporteerd. Een gebrek aan kennis ontbreekt echter op deze lijst met zelf-gerapporteerde barrières. Met het EVIDENCE-project beoogden we het kennisniveau van zorgverleners over evidence-based richtlijnen voor de preventie van zorginfecties na te gaan, en deze te helpen verbeteren indien deficiënties zouden worden gedetecteerd.

Als eerste stap in het identificeren van potentiële tekorten in de kennis van zorgverleners over dit belangrijk onderwerp werd een behoeftenanalyse uitgevoerd. Daartoe ontwikkelden we meerkeuzevragenlijsten aangaande de preventie van ventilatorgeassocieerde pneumonie, infecties gerelateerd aan het gebruik van centrale veneuze katheters, en chirurgische wondinfecties. De betrouwbaarheid van deze vragenlijsten werd nagegaan door middel van item analyse, en hun inhoud werd ter validering voorgelegd aan een panel experts. Vervolgens werden ze aangewend in een aantal surveys onder intensievezorgenverpleegkundigen. De resultaten van deze onderzoeken, waarvan twee gevoerd werden op Europese schaal, brachten algemene ontgoochelende test scores aan het licht die lager lagen dan de conventionele 50% drempel om te slagen voor een test.

E-learning werd gekozen als onderwijsmiddel om aan de geïdentificeerde noden tegemoet te komen. E-learning laat volwassen afstandsleerders immers toe te studeren waar en wanneer men verkiest, en aan eigen tempo. Door middel van open source software en in een begrijpelijke taal werd een op een website geënte *Crash Course* ontwikkeld die de basisbeginselen van de preventie van zorginfecties bundelt. Verschillende soorten oefeningen die studenten toelaten hun leerevolutie te evalueren werden in de cursus geïntegreerd. Om de toegankelijkheid van de cursus wereldwijd te faciliteren, is toegang tot een computer met internetbrowser de enige vereiste; bijkomende plug-ins of het downloaden van additionele software is onnodig. De inhoud van de cursus werd gevalideerd door een team experts op het gebied van infectiepreventie en de gebruiksvriendelijkheid en

technische adequaatheid werden getest en goed bevonden door middel van de Software Usability Measurement Inventory (SUMI®).

Om na te gaan of de cursus er daadwerkelijk in slaagt blijvende kennis bij te brengen, werd een studie-website gecreëerd waar alle betrokkenen in patiëntenzorg zich vrijwillig voor het studeren van de module konden registreren. Na het afleggen van een pretest werd hen gedurende een maximale periode van acht weken toegang tot de cursus verleend. De feitelijke studietijd van de participanten werd automatisch geregistreerd. Meteen volgend op de studieperiode werd een eerste posttest afgelegd om het onmiddellijk leereffect van de cursus na te gaan. Gedurende de twaalf weken na deze posttest werd aan de studenten de toegang tot de cursus ontzegd. Vervolgens werden de participanten uitgenodigd een tweede posttest af te leggen om de mate van kennisretentie te evalueren.

We vonden dat een beperkte tijdsinvestering in het studeren van de EVIDENCE *Crash Course* een significante onmiddellijke gemiddelde stijging van de kennis (+24%) en residueel leereffect (+18%) teweegbracht bij verpleegkundigen, artsen, studenten en andere zorgverleners. Hoewel de cursus oorspronkelijk ontwikkeld was voor zorgverleners tewerkgesteld in een setting voor kritieke zorg, bleken ook andere gezondheidswerkers er significant baat van te hebben.

Verder onderzoek dat focusseert op het vergelijken van verschillende e-learning interventies is nodig om klaarheid te scheppen in de vraag wat de beste manier is om e-learning te implementeren. Ondertussen zijn onze onderzoeksresultaten sterk suggestief voor het feit dat een matige tijdsinvestering in het instuderen van een met beperkte middelen gerealiseerde e-cursus met adequate gebruiksvriendelijkheid en geïntegreerde oefeningen voor zelfevaluatie de kennis over de preventie van zorginfecties significant kan verbeteren.

GENERAL INTRODUCTION

Healthcare-associated infections, and nosocomial infections in particular, constitute an important problem in acute care hospitals, and in the intensive care unit in particular. They are associated with significant excess morbidity and mortality, and generate additional costs for both the individual patient and society.[1] In recent years, the staggering gravity of the problem of healthcare-associated infections has led to a transition from accepting them as an inevitable outcome of hospital admission toward a goal of zero tolerance. Prevention of healthcare-associated infections has thus become a priority for which each healthcare professional is personally held accountable.[2-6]

Although not all healthcare-associated infections are preventable, many can be avoided. Up to 65%–70% of cases of central line-associated bloodstream infection and catheter-related urinary tract infection, and 55% of cases of ventilator-associated pneumonia and surgical site infection are esteemed to be preventable if current evidence-based strategies are applied.[7]

Striving to raise awareness of these important strategies, various authoritative organisations have graded their underpinning level of evidence, rephrased them into recommendations, and aggregated them into evidence-based guidelines, which were made widely available and easily accessible.[8-20] Unsolicited distribution of guidelines as such has however been proven not to change clinicians' practice,[21] which is reflected by the wide range of publications reporting on a lack of guideline compliance among healthcare professionals.[22-34]

The reasons for healthcare providers' non-adherence have mostly been investigated by means of surveys with a self-reporting design.[23, 34] As such, a large number of self-perceived barriers have been identified. Strikingly, a lack of knowledge of the guidelines' contents appears not to be part of the long list of self-reported hindrances. Knowledge gaps may however seriously jeopardize adherence. For, while knowledge does not open the door directly to compliance, it is undeniably a *conditio sine qua non*, a first requirement that is to be fulfilled.[35, 36] As such, education of healthcare personnel is widely acknowledged to be a fundamental and primordial measure to successfully reduce healthcare-associated infection rates.[37-43]

Scope and aim of the thesis

The present thesis reports on the EVIDENCE-project, a study that aimed to evaluate clinicians' knowledge of evidence-based guidelines for the prevention of nosocomial infection, and to help increasing the level of knowledge in case deficiencies were detected. As the focus was on the promotion of *evidence-based* care, the project was simply called EVIDENCE. It comprised a six-years period, starting on 1 November 2006 and ending on 15 July 2012.

The EVIDENCE-project included three major stages.

Phase 1: 2006 - 2009

In a first phase, we conducted a needs analysis in order to assess knowledge about evidence-guidelines for the prevention of ventilator-associated pneumonia, central venous catheter-related infection and surgical site infection among European intensive care nurses. For this purpose, we developed multiple choice knowledge tests that we took through the processes of validation and reliability testing. Subsequently, a network of national representatives was set up. These co-workers distributed the tests among nurses in their respective countries and mailed us all completed copies. Thus we obtained the test results of 3405 intensive care nurses from 22 European countries. Regrettably, the results revealed substantial knowledge gaps, illustrated by overall test scores below the conventional 50% threshold to pass a test.

Phase 2: 2009 - 2010

Alarmed by these poor results, we reflected about which resource could effectively and efficiently help enhancing knowledge. The literature revealed that e-learning has recently been acknowledged to be an important educational tool, which led us to develop a concise and interactive Web-based e-learning course that bundles the essentials on infection prevention in a comprehensible way. Thus, the EVIDENCE *Crash Course* saw the light.

Phase 3: 2010 - 2012

In the third and last phase of the EVIDENCE-project, we assessed whether our *Crash Course* would actually contribute to enhancing knowledge among distant learners by developing a study website and gathering an international sample of healthcare professionals who volunteered to study the course. Participants took three multiple choice tests: (1) a pre-test,

before accessing the course that aimed to measure baseline knowledge; (2) a first post-test, immediately after studying the course to evaluate the immediate learning effect; and (3) a second post-test twelve weeks after post-test 1 and without further access to the course to assess retention of the knowledge acquired.

The EVIDENCE study was reviewed and approved by the ethics committee at Ghent University Hospital.

Outline of the thesis

Although the main focus of this thesis is the EVIDENCE study, it simultaneously aims to provide the reader with the broader context in which the EVIDENCE project is to be situated. To meet this goal, it has been divided into three main parts.

Part one, *Evidence-based prevention of healthcare-associated infection*, aims to acquaint the reader with the background and core concepts of the EVIDENCE-project.

Part two, *Intensive care nurses' knowledge of infection prevention guidelines*, reports on the development of the multiple choice questionnaires and summarises the results of the needs analysis.

Part three, *E-learning*, introduces the reader to this resource chosen to develop the EVIDENCE *Crash Course* and reveals the study results related to the testing of the course's value in increasing and sustaining knowledge among healthcare professionals.

The outline of these three parts is specified in their respective introduction sections.

Publications included in the thesis

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PART ONE

EVIDENCE-BASED PREVENTION OF HEALTHCARE-ASSOCIATED INFECTION

"It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm."

Florence Nightingale (1820 - 1910)

Notes on Hospitals, 1863

Introduction

The first part of this thesis aims to create a framework that acquaints the reader with the broader context of the EVIDENCE-project. The reader is invited to explore the main concepts within the project throughout four chapters, that aspire to provide an adequate background for the interpretation of the study results, presented in parts two and three.

As the EVIDENCE-project focuses on healthcare-associated infection, the first chapter is dedicated to this staggering problem. Besides a description of the incidence and the adverse outcomes associated with their development, the need for initiatives aiming at their prevention is stressed.

Evidence-based recommendations are commonly bundled into guidelines, in order to optimally assist healthcare professionals in daily clinical decision making. The second chapter briefly introduces the concept of evidence-based guidelines, and lists a number of authoritative organisations that have been involved in the development and publication of evidence-based guidelines in the field of preventing healthcare-associated infection.

Chapter three focuses on the determination of the evidence base of such guidelines. In this thesis, two evaluation strategies are presented: grading the evidence of interventions using the Grades of Recommendation, Assessment, Development, and Evaluation System (GRADE), and performing a systematic review and meta-analysis of randomised controlled trials, respectively.

As adherence to guidelines among clinicians has been reported to be limited, a fourth and last chapter of this part is dedicated to the barriers and facilitators that respectively hamper or enhance compliance with recommendations.

1. Healthcare-associated Infections

1.1. Definitions

Healthcare-associated infection (HAI) is conveniently defined as an infection occurring in a patient in a hospital or other healthcare facility in whom the infection was not present or incubating on admission to that hospital/facility.[44, 45] The Centers for Disease Control and Prevention (CDC) define HAI more specifically as a localized or systemic condition resulting from an adverse reaction to the presence of (an) infectious agent(s) or its (their) toxin(s), for which there must be no evidence that the infection was present or incubating at the time of facility admission.[46]

In most cases, these definitions imply that the infection becomes manifest 48 hours (i.e., the typical incubation period for bacterial infections) or more after admission. Incubation periods, however, vary with the type of pathogen involved, and to some extent also with the patient's underlying condition. Therefore, for each infection an individual assessment must be conducted to evaluate whether it is to be linked to the hospitalisation as such.[47]

Nosocomial infections are a subset of healthcare-associated infections. Also known as hospital-acquired infections, they refer to infections patients acquire in hospital settings. Since 2008, the CDC uses the generic term *health care-associated infection* instead of *nosocomial*.[46]

In the intensive care unit (ICU), the *Big Four* infection types that account for more than 80% of all HAIs are ventilator-associated pneumonia (VAP), central venous catheter-related bloodstream infection (CVC-RI), surgical site infection (SSI) and catheter-related urinary tract infection (CAUTI).[48]

VAP is defined as pneumonia developing more than 48 to 72 hours after initiation of mechanical ventilation.[10, 49-51]

In the context of this thesis, CVC-RI refers to any type of infection that has developed secondary to the presence of any central venous catheter. This could include but is not limited to, localized tissue infection at the catheter site, catheter-related bloodstream infection, metastatic infection, or colonization.

Surgical site infections are infections that develop in patients who underwent surgery. The following classification has been proposed by the Centers of Disease Control and Prevention:[52] superficial incisional SSI, involving the skin and the subcutaneous tissue; deep incisional SSI, involving deep soft tissue layers, such as the fascial and muscle layers, of the incision; and organ/space SSI, involving any part of the anatomy, other than the incised body wall layers, that was opened or manipulated during the operation. Thereby, the specific organ or space involved is included as part of the definition to further identify the location of the infection.

Catheter-associated urinary tract infection refers to the presence of microorganisms that have invaded the bladder of a patient with an indwelling catheter.

For extensive information and detailed definitions we refer to the CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care settings.[46]

1.2. Epidemiological data

Affecting 5% to 10% of hospitalized patients in acute care hospitals, nosocomial infections are the most common type of complication hospitalised patients in Europe and the United States have to face.[1, 47] In developing countries, the problem is even more important with up to 50% of hospitalised patients affected.[45]

The ICU is the “hot zone” of nosocomial infections.[53] Critically ill patients often suffer immune depression induced by their condition or their medication, may have significant comorbidity, and mostly require multiple invasive devices that bypass natural host defences. It is therefore not surprising that HAIs affect up to 33% of ICU patients.[1, 53, 54]

In 2002, it was estimated that in the United States 1 737 125 nosocomial infections occurred. Of these, 561 667 were due to urinary tract infections, 290 485 to SSI, 250 205 to pneumonia, 248 678 to bloodstream infections, and 386 090 to other causes. The estimated annual deaths due to HAI amounted to 98 987.[55]

The more recently and world-wide conducted Extended Prevalence of Infection in Intensive Care (EPIC II) study was a one-day prospective point prevalence investigation that took place in March 2007 and gathered extensive data of 14 414 patients in 1265 participating ICUs from 75 countries. This major initiative revealed that 7087 of 13 796 patients analysed (51%)

were considered infected on the study day. Infections were demonstrated to be common in ICU patients, and risk of infection to increase with duration of ICU stay. It should however be acknowledged that, unfortunately, the EPIC II study suffered from methodological limitations, which impeded clear-cut distinction between community-associated and healthcare-associated infections.[56]

In 2008, Vrijens and colleagues[47] conducted a prevalence study of nosocomial infections in Belgian acute hospital settings. They found that the crude prevalence rate of patients infected was 6.2% (95% CI 5.9% - 6.5%), and the prevalence of infections 7.1% (95% CI 6.7% - 7.4%). Overall, the most prevalent infections were shown to be UTI (23.9%), lower respiratory tract infection (20.1%), SSI (14.6%) and bloodstream infections (BSI; 13.6%). In the ICU, the prevalence rate of patients infected added up to 25.3% and the prevalence of infections to 31.3%. Unsurprisingly, the most frequently diagnosed infections were lower respiratory tract infections (15.9%), BSI (6.20%), SSI (2.69%) and UTI (2.22%).[47]

Additional epidemiological data on specific infection types are reported in the respective introduction sections of the papers included in Part Two of this thesis.

1.3. Impact

The impact of HAIs in terms of excess morbidity, mortality and expenditures is known to be detrimental.[57-59] A study of 1 355 347 admissions in 55 US hospitals from 2001 to 2006 estimated that each nosocomial infection increased medical costs by $12 197.[60] According to a publication from the United Kingdom, the average increased medical cost for each central venous catheter infection was £6200,[61] and in a Belgian study dated 2005, hospital-acquired bacteraemia was estimated to increase medical costs by an average of €12 853.

More recently, Vrijens and colleagues estimated excess mortality, length of stay and costs attributable to HAIs in acute care hospitals in Belgium.[62] A matched cohort design with the six following matching factors was used: hospital, diagnosis-related group, age, ward, Charlson score,[63] and estimated length of stay prior to infection.[62] This study revealed an excess mortality of 2.8% and an excess length of hospital stay of 7.3 days. The related public healthcare cost calculated was €290 million.[62]

In US hospitals, it is estimated that the approximately 2 million HAIs occurring each year are associated with nearly 100,000 deaths.[1]

1.4. Prevention

Due to the detrimental impact of HAIs, their prevention has been acknowledged a priority on a worldwide scale. Only quite recently though, HAIs are no longer accepted as an inevitable outcome of admission to the hospital. Today, a culture of zero tolerance and personal clinician accountability toward these infections are globally promoted.[2-6]

This turnaround largely owes to the growing focus on improving patient safety over the past few years, particularly promoted in the US by the Institute of Medicine (IOM) and the Institute of Healthcare Improvement (IHI). The IHI made the institution of practices to prevent HAIs (specifically SSI, CVC-RI and VAP) three of the six *planks* of their 100,000 Lives Campaign (2004 – 2006), and kept this focus in their subsequent 5 Million Lives Campaign (2006 – 2008).[6, 64]

Moreover, public reporting of infection rates in the US has been implemented as a means of informing the public and encouraging preventive efforts, with legislation requiring some type of reporting in the majority of states.[65] Although transparency and public education have met with resistance, they now have the support of major national medical organizations.[66] As a further initiative to promote quality, the American Centers for Medicare and Medicaid Services have proposed the installation of financial implications such as policies that decline payment in the event of preventable hospital-acquired conditions.[2, 4, 66] Following the example set in the US, the prevention of healthcare-associated infection has become a priority in most healthcare settings worldwide.

Although not all HAIs are preventable, many can be avoided. A systematic review of 30 reports published between January 1990 and October 2002 found that a minimum reduction effect of 10% and up to a maximum effect of 70% could be obtained, depending on the setting, study design, baseline infection rates and type of infection.[67] The authors concluded by considering at least 20% of all nosocomial infections as probably preventable.[67]

Another, more recent, estimation of the preventable proportion of HAI by Umscheid and colleagues considers up to 65%-70% of cases of central line-associated bloodstream infections and CAUTI, and 55% of cases of VAP and SSI to be avoidable.[7]

Successful HAI prevention requires healthcare workers to follow the most recent evidence-based recommendations.[7] Moreover, and as illustrated by the examples below in the field of

preventing CVC-RI, a multidisciplinary approach has been shown to yield excellent results in reducing HAI rates.[68-73]

Among the most appealing examples of successful HAI prevention, are a series of very fine studies using a well-defined set of multifaceted preventive strategies to reduce CVC-RI rates in the ICU, taken from the CDC guidelines[17] for preventing catheter-associated infection.[69, 70, 74] This set, which has been shown to be utmost effective, consisted of the following five multidisciplinary interventions: (1) education of the local staff; (2) creation of a catheter insertion cart; (3) daily assessment of the need for the catheter to remain in situ; (4) implementation of a checklist to ensure adherence to evidence-based CVC-RI prevention guidelines; and (5) empowerment of nurses to stop catheter insertion if breaches in the procedure are detected.

Applying this set of interventions in a surgical ICU, Berenholtz and colleagues report a decrease of the rate of CVC-related bloodstream infections over a five-year time period from 11.3 to zero per 1000 catheter days. The authors estimate that the interventions may have prevented 43 CVC-related bloodstream infections, eight deaths, and $1 945 922 in additional costs per year.[69]

Using the same five strategies, Pronovost et al. report their study results obtained from 103 intensive care units, including 1981 ICU-months of data and 375 757 catheter-days.[70, 74] They describe a decrease in the median rate of catheter-related bloodstream infection per 1000 catheter-days from 2.7 at baseline to zero at three months after implementation of the study intervention ($p<0.002$), and a decrease in the mean rate per 1000 catheter-days from 7.7 at baseline to 1.4 at 16 to 18 months of follow-up ($p<0.002$). The regression model demonstrated a significant decrease in infection rates from baseline, with incidence-rate ratios that continuously decreased from 0.62 (95% CI 0.47 - 0.81) at zero to three months after implementation of the intervention to 0.34 (95% CI 0.23 - 0.50) at 16 to 18 months.[70, 74]

These and other reports[37, 38, 41, 42, 71, 75-79] on the successful implementation of initiatives to reduce HAI rates clearly indicate that prevention works, and that intensive and sustained multidisciplinary efforts are truly worthwhile.

2. Evidence-based Guidelines

Based on the book chapter: Labeau S, Vandijck D, Blot S. Implementation strategies for the prevention of healthcare-associated infection. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine 2010*. Berlin: Springer; 2010: 244-256.

2.1. Definition

Evidence-based guidelines are guidelines which are founded on a critical appraisal of the available scientific evidence, clarifying which interventions are of proved benefit, and documenting the quality of the supporting data. They alert clinicians to interventions which are not supported by good science, reinforce the importance of critical appraisal, and advise against ineffective and dangerous strategies.[80]

With the rise of the concept of evidence-based medicine since the early 1990s, worldwide, various ambitious programs for guideline development have been invested in. Simultaneously, however, numerous more modest and local guideline development initiatives also arose. The subsequent proliferation of recommendations and concerns about their quality and uniformity have led to the foundation of public resources for evidence-based clinical practice guidelines, such as the United States' National Guideline Clearinghouse, and to international collaborations, such as The Guidelines International Network, that released the International Guideline Library, a searchable database which now contains more than 2000 guideline resources.[81]

In the field of preventing HAIs, various authoritative organisations and research groups have issued evidence-based guidelines, which they made readily available for healthcare workers to consult. These organisations include, among others, the US Centers for Disease Control and Prevention (CDC),[14-20] the American Thoracic Society,[10] the Association of Medical Microbiology and Infectious Diseases Canada,[11] the Canadian Critical Care Trials Group of the Canadian Critical Care Society,[12] the UK National Institute for Health and Clinical Excellence,[8, 13] and the UK Department of Health.[9] Guidelines pertain to the prevention of VAP,[10, 12, 18, 82-87] CVC-RI,[15, 17, 88] SSI,[13, 20, 89] UTI[19, 90-93] or to the prevention of HAIs in general.[8]

Beside the guidelines issued by separate organisations or research groups, joint initiatives in developing and publishing evidence-based HAI prevention guidelines were taken.[94, 95] Such joint efforts of the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America Standards and Practice Guidelines Committee have led to the publication of a compendium of recommendations for HAI prevention. This compendium differs from most previously published guidelines in that it is typically implementation-focused.[1, 3]

2.2. Guideline implementation

In recent years, there is a growing awareness of the fact that published guidelines are not self-implementing. Unsolicited distribution of guidelines as such has been proven not to change clinicians' practice.[21] Active and sustained implementation efforts in the healthcare setting are required before guidelines can be expected to actually influence clinicians' behavior.[26, 96] Transferring research findings into healthcare professionals' daily practice is a slow and laborious process[97, 98] that may be facilitated and supported by the findings of implementation research.

Implementation research is defined as the scientific study of methods to promote the uptake of research findings, and hence to reduce inappropriate care. It includes the study of influences on healthcare professionals' behavior and interventions to enable a more effective use of implementation-related research findings.[99] Implementation research requires a multidisciplinary collaboration between healthcare professionals.[100, 101]

Guideline implementation is the phase in the guideline lifecycle in which strategies, systems and tools are created to operationalize the knowledge and recommendations set forth by the guideline developers.[102] Guideline implementation is thus the final step in translating the scientific basis into clinical practice.

2.2.1. Implementation strategies

An *implementation intervention* or *implementation tool* is a single method or technique to assist a proposed change. In the literature, these interventions are also referred to as *uptake*, *adoption*, or *change interventions*. An *implementation strategy* or *implementation*

program is defined as an integrated set (bundle, package) of implementation interventions.[103]

The following classification of strategies for guideline implementation has been proposed.[6]

1. Clinician education (e.g. workshops, (computerized self-study tutorials, …)
2. Patient education (e.g. pamphlets, classes, …)
3. Audit and feedback (e. g. benchmarking, quality reports, …)
4. Clinician reminder systems (e. g. in charts or computer-based, …)
5. Organizational change (e. g. increased staffing, multidisciplinary teams, …)
6. Financial or regulatory incentives for patients or clinicians

The current insights in implementation interventions and strategies have greatly been based on implementation research that was conducted since the early 1990's.[104-106] During the course of years, the research focus clearly moved from evaluating the effect of isolated interventions to determining the impact of bundle approaches.[1] Today, it is generally acknowledged that using only one type of implementation intervention is not likely to generate successful results, and that implementation efforts should use a combination of strategies tailored to the setting.[36, 98, 107]

<u>The 1990's</u>

As early as in 1994, when the rise of evidence-based medicine was still on-going, Haines and Jones denounced the unacceptable delays in the implementation of research findings.[108] They promoted a number of approaches which they considered to be effective in speeding up implementation, including the influence of opinion leaders and the use of computer-based decision support systems. Typical of the optimistic expectancies towards the implementation-promoting capabilities of evidence-based guidelines in that period, guidelines as such are mentioned among the implementation interventions that are considered to be potentially successful. The authors concluded that methods for improving the implementation of research findings required further investigation and greater resources devoted to them.[108]

An early review on implementation strategies was conducted by Wensing in 1998.[109] It covered a systematic literature study involving the period from January 1980 until June 1994 using MEDLINE in association with a manual search of 21 medical journals. By selecting

randomised controlled trials and controlled before-after studies, 61 studies covering 86 intervention groups that could be compared with a control group without the intervention, were included. The review aimed to identify the effects of different single and multifaceted interventions to implement guidelines or innovations in general practice by first comparing different single interventions with no intervention, and then comparing different multifaceted interventions with no intervention. Given the wide range of outcome measures, it was impossible for the author to identify a standardized outcome measure that could be compared across all studies. The predominant finding of the review thus was that there was a considerable variation in effectiveness among the different interventions included. The combination of information transfer and learning through social influence or management support was shown to be possibly effective, and so were reminders and feedback. Information transfer is probably always needed at some point in the process of implementing change, but more interventions appeared to be usually needed to achieve real changes in the practice routines of clinicians. Other interventions were also shown to have a potential beneficial effect, but the author reported to be unable to pronounce upon their effectiveness as further investigation remained required. The results of this analysis are to be treated with caution, especially because of the rather poor methodological quality of the studies included.[109]

On 5 and 6 October 1999, a group of implementation experts from Europe and the United States was convened at Leeds Castle, England, to identify the best ways to encourage and undertake the implementation of best practices. The subsequent meeting summary expresses the experts' common belief that the approach towards implementing a guideline should be multifaceted.[96] They suggest that the implementation process can be facilitated by recruiting the help of local opinion leaders, involvement of all stakeholders, broad dissemination of the objectives, and local consensus conferences. Reluctant converts or larger groups could be reached by means of academic detailing, while computer-aided decision support systems, reminders, and audit and feedback were considered to be useful in supporting clinicians' implementation efforts.[96]

The 2000's

In 2001, the available systematic reviews of interventions that potentially influence healthcare professionals' behavior change were investigated and discussed by Grimshaw

and colleagues.[43] The authors identified 41 reviews, covering a broad variety of interventions and behaviors. The quality of the included manuscripts showed, again, to be variable, and some methodological flaws were noticed. In general, passive implementation approaches such as passive dissemination, were found to be ineffective and unlikely to change behavior, while active approaches showed to be more likely to be effective, but only under certain circumstances. The latter are, nevertheless, also likely to be more costly. Among the active approaches, educational outreach and reminders are described as promising interventions, and multifaceted strategies targeting different barriers to change are considered to be more effective than single interventions.[43]

In 2004, a systematic review focussing on the effectiveness and costs of different guideline development, dissemination and implementation strategies included a total of 235 studies, which described 309 comparisons.[110] Of these, 73% evaluated multifaceted strategies. Overall, the majority of comparisons reporting dichotomous process data observed improvements in care. However, considerable variation in the observed effects, both within and across interventions, was reported. Frequently assessed single interventions were reminders, dissemination of educational materials, and audit and feedback. No relationship was found between the number of interventions included in bundle strategies and the strategies' effect. As a conclusion, the authors found an imperfect evidence base to support decisions about which guideline dissemination and implementation strategies are likely to be efficient under different circumstances. They state that further research is required to develop a validated theoretical framework on behavior and behavior change in order to make an informed choice of interventions and implementation strategies in the presence of different barriers and effect modifiers.[110]

Current insights

A 2008 synthesis of systematic review findings by Prior and colleagues concerning the effectiveness of guideline implementation strategies covered the period from 1987 to 2007, thus reflecting more recent insights.[107] Here, 33 reviews concerning 714 primary studies involving 22 512 clinicians in various healthcare settings were analysed. Implementation strategies were found to be wide-ranging, rarely comparable, and to have variable outcomes. The effectiveness of educational strategies, generally labelled as continuing medical education, is suggested to be controversial while traditional educational strategies,

typically including passive information dissemination, showed to be constantly ineffective. Interactive educational strategies such as workshops and practical sessions coupled with evaluation processes were persistently reported as effective, with improvement effects ranging from 1% to 39%. For educational outreach a relative improvement up to 68% in process or compliance was reported, while audit and feedback were associated with a range from no effect over a 17% decline to a 63% improvement. Multifaceted intervention strategies consistently resulted in significant improvements in guideline compliance and behavioral change, with a reported effect of improvement ranging up to 60%. Multifaceted interventions showed to have greater evidence of effectiveness than single intervention strategies. Similar to the 2004 findings by Grimshaw et al.[110] there was no evidence of any relationship between the number of components of a strategy and the strategy's effectiveness, neither was there any evidence for the effect of combined strategies. The value of mass media strategies remained inconclusive. Clinicians' behavior seems to be influenced by the construction and content of the guideline, with complex guidelines being inversely related to compliance. Trustworthiness of the developing organization and/or reference group showed to improve compliance, and so did the levels of evidence upon which guidelines were based. The use of reminders and clinical support systems demonstrated to be associated with considerable practice enhancements, while the effect of financial incentives was inconclusive. There was no consistent evidence that guideline adherence could be promoted by involving local opinion leaders.[107]

This review's overall findings are consistent with these of another 2008 systematic review on guideline implementation strategies in allied health professions[36] and reflect the general consensus that today no clear evidence is available to support a specific set of guideline implementation interventions that might be most effective and efficient in the field of healthcare.

2.2.2. Implementation of infection prevention guidelines

The lack of certainty about the most effective strategies for guideline implementation also pertains to the field of guidelines for preventing and controlling infection. Until today, only few resources are available that provide healthcare professionals with clear guidance regarding effective implementation interventions and strategies specifically focused on this field.[1]

Interventional studies

Numerous studies using a broad range of strategies and reporting varying results have been published related to the implementation of evidence-based guidelines for preventing infection.

In the field of preventing infections associated with the use of central venous catheters, the studies by Berenholtz and colleagues[69] en by Pronovost and colleagues[70, 74] have been discussed previously in this thesis to illustrate the successes obtained through multifaceted implementation programmes.

To implement evidence-based guidelines for preventing VAP in a surgical ICU, an electronic dashboard, serving as a screen saver on every desktop computer, was used.[111] The left side of the screen indicated patient demographics and provided access to the medical records, while evidence-based preventive measures were indicated at the right hand side of the screen. Colour indicators green, red and yellow were used to mark the degrees of measures in compliance. Over a one year period, mean compliance with the recommendations improved from 39% to 89% ($p<0.001$), and VAP rates decreased from a mean (standard deviation) of 15.2 (7.0) to 9.3 (4.9) per 1000 ventilator days after introduction of the dashboard ($p=0.01$).[111]

Next to numerous success stories, a number of studies were published that demonstrate a failure to implement evidence on infection prevention and control into daily practice. Examples of such less successful implementation reports are provided by Morse et al., where the single use of a poster-based education programme to improve the recording of date and time of insertion of peripheral venous catheters was shown to have little effect,[112] and by De Miguel-Yanes et al., who report on a failure to implement evidence-based clinical guidelines for sepsis at the emergency department.[113]

Although single studies may be suggestive and inspiring, they do not provide the healthcare worker with a global view of which (set of) implementation intervention(s) may be most beneficial.

Systematic review

Recently, more bundled information was provided by the Stanford-UCSF (University of California San Francisco) Evidence-based Practice Center, that reviewed the literature on effective implementation of measures to promote adherence to guidelines for the

prevention of VAP, SSI, CVC-RI and CAUTI.[6] The authors aimed to identify (1) the implementation strategies that effectively increase adherence to evidence-based preventive interventions for healthcare-associated infections; (2) the critical components of effective quality improvement strategies; and (3) the limitations of the current research in this specific area. Sixty-four studies met the inclusion criteria: 28 studies addressed the prevention of SSI, 19 of CVC-RI, 12 of VAP, and 10 studies focused on CAUTI prevention. Three additional studies targeted prevention of multiple HAIs. The strategies that demonstrated to be effective in implementing evidence-based guidelines for the prevention of the respective HAIs are summarized below.

SSI

The limited data suggests that educational interventions combined with audit and feedback may be effective at improving adherence to evidence-based recommendations for SSI prevention, specifically appropriate antibiotic prophylaxis. Clinician reminders may also be effective, especially when incorporated into a computerized physician order entry system. No conclusion could be reached regarding the effectiveness of educational interventions alone. The effect of using audit and feedback is not clear.

CVC-RI

Active educational interventions showed to reduce the incidence of CVC-RI. These interventions used demonstrations and self-study tutorials to improve adherence to evidence-based prevention guidelines during line insertion. The use of a checklist during the insertion procedure, and empowerment of nurses to stop catheter insertion whenever a violation of the procedure was noticed, resulted in marked reductions in infection rates.

VAP

Active educational interventions with the use of a self-study module for ICU staff, including web-based and video tutorials, appear to be a promising strategy for reducing VAP rates. No conclusion could be reached on the effectiveness of audit and feedback or other implementation strategies on VAP rates.

CAUTI

Printed or computer-based reminders to clinicians appear to be effective in reducing unnecessary catheter usage. A key element of these studies was the use of an automatic stop order, mandating discontinuation of the catheter after a specific time period (48 to 72

hours) unless the physician countermands the order. The effect of other implementation strategies on either infection rate or process measures could not be determined.

In all included studies, information concerning potential adverse effects of the implementation strategies was extremely scarce, and so was high quality data concerning cost-benefit assessments. The reviewers' conclusion is twofold: (1) preliminary data suggests that a number of implementation strategies are worthy of future investigation, and possibly wider implementation, and (2) higher quality studies of implementation strategies to implement preventive evidence-based recommendations are urgently needed. Due to the poor quality of included studies and the limited number of controlled trials, the authors were unable to perform any quantitative analyses, thus being unable to make any estimate of the effect size expected when implementing these strategies, nor any firm recommendation.[6]

A rather new and innovative implementation strategy is the so-called bundled approach,[64] which was introduced by the IHI's two subsequent major campaigns for the promotion of patient safety, i.e. the 100,000 Lives Campaign (2004 – 2006) and 5 Million Lives Campaign (2006 – 2008).[64] A care bundle is defined as a small set of evidence-based practices, usually three to five, that individually have been proven to improve patient outcomes, and that are expected to result in a better outcome when implemented together than when implemented separately.[114, 115] All recommendations included in a bundle should be respected by all healthcare workers, at all times, and for all eligible patients. Therefore, bundles are often referred to as a 'all or nothing'-strategy. The first care bundles created by the IHI were the ventilator bundle and the central line bundle, focussing on the prevention of complications in mechanically ventilated patients and of CVC-RI, respectively. In the time to follow, various bundles for a plethora of conditions have been developed worldwide.[2, 85, 115-128]

Fulbrook and Mooney[129] describe a seven-step process to develop a care bundle. The first and second step are the identification of a care theme, and a cluster of generally recognized practices or interventions within that theme, respectively. The third step consists of performing comprehensive and systematic literature searches in each of these areas. This review should not be limited to the search of scientific electronic databases but should also include the 'grey' literature, such as research abstracts and meeting proceedings. The fourth

and fifth step comprise an extraction and the reading and categorizing of the quality of evidence, respectively. Identification and clarification of the solidity of the evidence base is recognized to be the most challenging step in the bundle development process. In step six, all interventions lacking a solid evidence base are to be discarded. Finally, an appropriate clinical protocol can be drafted on the basis of the analysed research evidence. It is elementary that this protocol clearly outlines that it relates to a grouping of components, which should be practiced together at any time and by all healthcare professionals concerned.[129] Inherent to the bundle concept is that bundle becomes obsolete when new or stronger evidence becomes available. Therefore, periodical systematic reviews of the related literature and timely updates of the bundle components are required.

Various prospective studies have identified a positive relationship between patient outcomes in term of HAI prevention and bundle compliance.[70, 74, 115, 119] Reviews investigating HAI prevention bundle effectiveness also yielded overall positive conclusions,[130-133] but due to the limitations of the observational designs used in the studies retrieved, a definitive causal relationship between bundle use and reduction of infection rates cannot be stated today.[131] However, the evidence to date is strongly indicative of a positive association.[131]

2.2.3. Evaluating the implementation

Evaluating an implementation consists of assessing whether or not the efforts have been effective when measured against the objective. A good evaluation comprises both the process and the outcome of the strategies used.

A process evaluation consists of an examination of the approaches used to achieve the objective. While this process evaluation is important, it is a 'surrogate' endpoint only and the evaluation of outcomes should definitely not be forgotten.[134] Evaluating the outcome is more difficult than evaluating the process, and requires a fair degree of planning. It also requires a budget and assigned personnel to carry out the task.[134]

2.2.4. Sustainability of implementations

While initial implementation efforts have quite extensively been studied, less research has been dedicated to the sustainability of such innovations.[135, 136]

A prerequisite to studying sustainability is a clear understanding of the concept. According to Bowman et al.[136] sustaining improvements refers to holding the gains made during the implementation phase of a project that typically provides a generous supply of support for the intervention in terms of personnel and other resources, for a variably defined period after the funding has ceased and project personnel have been withdrawn. As such, a program or intervention's impact may be considered sustained if desired health benefits remain at or above the level achieved during implementation and this increase can be attributed to continuation of the program.[137] A program or intervention may be considered to be sustained at a given point in time if, after initial implementation support has been withdrawn, core elements are maintained and adequate capacity for continuation of these elements is maintained.[137] This conceptualization implies the necessity of defining a timeframe adequately beyond an initial implementation effort in order to provide meaningful evidence.

Shediac-Rizkallah and Bone[138] propose the following categories of operational indicators to monitor sustainability over time: (1) maintenance of health benefits achieved through an initial program, (2) level of institutionalization of a program within an organization and (3) measures of capacity building in the recipient community.

Wiltsey Stirman et al. conducted an extensive review of the English language literature, published or in press by July 2011, to determine the methods used to study sustainability of implementation efforts, the types of outcomes measured and reported, factors identified as potential influences on the sustained use of new practices, programs, or intervention, and findings from studies reporting long-term implementation outcomes.[137] A total of 460 published articles were identified, of which 125 met the inclusion criteria and were selected for the review. Although of considerable interest, a comprehensive report of all findings within this review is beyond the scope of this thesis. Below, only the results related to long-term implementation outcomes and their potentially influencing factors retrieved from medical, public health/health promotion, and mental health studies are briefly reported.

As a noteworthy general finding, partial sustainability appeared to be more common than continuation of the entire program or intervention, even if full implementation was initially obtained. In general, not all aspects of the originally implemented program were maintained over time, with only very few studies elaborating on the nature of the adaptations made, the reasons for changes, or the process by which decisions to discontinue elements of the original program were made. It is well known indeed that studying sustainability of implementation efforts may be hindered by the fact that interventions as originally designed often need adaptation when used in specific settings or contexts that substantially differ from those in which they were developed. Today, however, few procedures or benchmarks are available to identify the extent to which interventions were continued as implemented.[137] Multilevel measurement of sustainability, based on sound conceptualization, would allow for greater methodological rigor and interpretability of findings.[139] This finding also stresses the importance of the recommendation by Bowman and colleagues[136] that implementation scientists should keep the longer view in mind when designing interventions, including those that potentially will be exported to other contexts.

The review identified a wide range of outcomes.[137] Few studies based on independent observation validation reported high rates of continuation at the site or setting level. Those reporting on full sustainability at the provider level identified less than half of the observed providers sustaining the implemented interventions at a high level of skill, intensity, or fidelity. Seventy-five studies related changes in implementation or recipient-level outcomes after initial implementation efforts or funding had ended, of which 56 reported on the intervention or program implementation. Of the latter, 19 described lower levels of implementation following the initial implementation efforts, 17 reported an increase, and 3 mentioned no change. Varying changes in rates across different program components were identified in 17 studies.

In 22 studies, changes in outcomes were evaluated, 5 of which reporting a decrease in desired outcomes, 10 an increase, and 1 reported no change. The remaining five studies reported multiple outcomes or indicators with varying extents of durability.

The authors identified four categories of factors that have a potential influence on the achievement of long-term implementation: (1) influences related to the innovation included the fit of the innovation for the local context, its ability to be modified according to local

needs, its effectiveness or benefit, and its ability to maintain fidelity or integrity; (2) influences related to the organizational context comprised culture, climate, leadership, specific characteristics of the setting such as structure and policies, and system or policy change; (3) influences related to the (internal and external) capacity were workforce, funding, resources, champions, and the involvement and / or support of stakeholders and the community; (4) influences related to the processes and interactions, finally, included engagement/relationship building, shared decision making among stakeholders, adaptation, integration of rules or policies, evaluation and feedback, training and education, collaboration/partnership, navigating competing demands, on-going support, and planning.

When aiming to achieve long-term effects from implementation efforts, the findings of this review[137] could be a helpful source of information. Importantly, however, it should be noted that relatively few of the studies included were assessed as comprehensive or methodologically rigorous. Mostly, no operational definition of sustainability was provided, and in less than 50% a published definition or model of the concept was used. These limitations as well as the variety of results reported did not allow the authors to generalize their findings.

2.2.5. Cost considerations

Studies and reviews concerning the effectiveness of implementation interventions and strategies are numerous, but economic evaluations of guideline implementation strategies are scarce. Developing and implementing guidelines, however, can be quite costly. Sometimes, implementation costs are even likely to prevail over the potential benefits, and organizations should consider that the implementation of less costly -but also less effective- implementation strategies might be more efficient in their setting.[140]

The economic aspects of 63 out of 235 studies on guideline implementation[110] were commented by Vale and colleagues.[140] Of these, only 3 studies provided evidence that their guideline was effective and efficient; 38 reported treatment costs only, 12 implementation and treatment costs, 11 implementation costs only, and 2 reported on guideline development, implementation and treatment costs. None of the studies provided complete information on costs. The type of economic evaluation was rarely mentioned, and if it was, it was sometimes unclear. Seldom all relevant costs and benefits were included. Overall,

studies were of poor methodological quality, did not report an economic rationale for the choice of implementation strategies considered, nor did they cover all potentially relevant stages of guideline implementation. The multifaceted nature of various implementation strategies in the primary studies, the broad variety of strategies addressed and the weak methodology of most evaluations included made it impossible for the reviewers to generate a structured and uniform report of outcomes.[140]

An earlier mentioned review by Prior and colleagues, summarizing the evidence of effectiveness of clinical guideline implementation strategies in terms of improved clinical processes, also took into account the effectiveness in terms of cost-benefits.[107] Also in this report the authors remark that, although increased cost-efficiency is a frequently cited reason for implementing clinical guidelines, only few systematic reviews report primary studies that investigated financial outcomes. For most guideline implementation strategies in these reviews, significant cost reductions in clinical practice were reported, but it was not known whether the benefits were offset by the costs of the implementation strategies. This lack of economic evaluation is referred to as a major detractor from the widespread uptake of guidelines, particularly as it has been suggested that, due to the provision of services advocated as *best practice*, healthcare costs may increase.[107]

2.2.6. Methodological considerations

All systematic reviews discussed in the above sections are limited in the generalization of their findings due to some considerable methodological weaknesses of the publications included. A striking but valid illustration of this problem is provided through the bold statement by Bowman and colleagues that "… methods used in evaluating the success of implemented QI [quality improvement] interventions and strategies are 'messy' at best …".[136] To reach the goals of implementation science, strong methods are needed indeed to develop a solid knowledge base.

In some cases, implementation science can rely upon rigorous tools and methods used in efficacy and effectiveness research. For example, an examination of the impact of implementation features on fidelity can be assessed by means of randomized controlled trials. In other cases, the adequate assessment of major nuances in implementation might need reconsideration of established methods. As such, achieving adequate sample sizes and

maximizing power may present challenges when small settings are involved. Finally, new tools and measures may be needed to address the questions of specific relevance to implementation science.[141]

Depending on the specific research focus, a wide range of research methodologies can be employed. Randomised controlled (multi-center) trials are often required to evaluate the (cost-)effectiveness of specific strategies and programmes, while qualitative and observational research have their value in identifying problems in creating change and generating hypotheses about the determinants of and the conditions for change. Economic analyses are needed to assess the efficiency of implementation efforts. Psychometric studies, in turn, are required to determine the value of indicators and criteria for evaluating the success of implementation. Follow-up studies and continuous monitoring of successes and failures obtained are needed as well.[100]

Some general recommendations that might contribute to a more methodological rigour of implementation research include:

- the use of a clear and established conceptual framework;[142]

- the selection of study designs tailored to the specific research question;

- the use of mixed methods: mixed methods designs focus on collecting, analysing and merging both quantitative and qualitative data. The central premise is that the use of these approaches in combination provides a better understanding of research issues than either approach alone;[143]

- the integration of a sustainability assessment to determine long-term effects of the implementation, including both formative and outcome evaluation.[137]

3. Determining the Evidence Base of Recommendations and Strategies

A characteristic of evidence-based guidelines is that they document the quality of the supporting data. They do so by assigning to each recommendation a certain grade, that reflects the strength and the soundness of the body of evidence by which it is supported.
The supporting evidence is indeed not equally strong for all available recommendations. Sometimes, it is very clear that a specific preventive strategy is absolutely superior to others; at other times, nevertheless, the current state of the science has not succeeded yet in determining which of different strategies is most (cost-)effective.
The strength of a recommendation is thus determined by the body of evidence by which it is supported. Below, some basic information is provided concerning two ways by which the strength of the supporting body of evidence of individual interventions can be determined: (1) by systematically grading the evidence of separate published strategies and (2) by conducting a systematic review and meta-analysis.

3.1. Grading the evidence of interventions

Based on the article: Aitken LM, Williams G, Harvey M, Blot S, Kleinpell R, Labeau S, Marshall A, Ray-Barruel G, Moloney-Harmon PA, Robson W, Johnson AP, Lan PN, Ahrens T. Nursing considerations to complement the Surviving Sepsis Campaign guidelines. Crit Care Med. 2011;39(7):1800-1818.

In the course of the last three decades, a plethora of systems to grade the evidence base of published interventions has been developed,[144] the first of which was issued in 1979 by the Canadian Task Force on the Periodic Health Examination.[145] Since then, various alternative approaches have been proposed.[145] All aim to inform clinicians about the strength of the evidence of published interventions, and to assist healthcare workers in daily clinical decision-making by rephrasing the results of the grading process into recommendations.

Below, the results of such grading process is illustrated by an initiative that aimed to determine which nursing considerations would most effectively complement the recommendations for physicians outlined in the Surviving Sepsis Campaign.[146] Thereto, the evidence base of eligible interventions and strategies was assessed by an international group using a modified Delphi method and the Grades of Recommendation, Assessment,

Development, and Evaluation System (GRADE). With the GRADE system, the quality of evidence is rated from high (A) to very low (D), and the strength of recommendations is determined: GRADE 1 indicates clear benefit and GRADE 2 indicates less confidence in the benefits of the intervention.

Table 1 demonstrates the GRADE criteria utilised in the review process.

Table 1: The GRADE criteria[147, 148]

Strength of Evidence	**Quality of Evidence**
1 – Strong	A – high, e.g. well conducted RCT
2 – Weak	B – Moderate, e.g. downgraded RCT or upgraded observational studies
	C – Low, e.g. well done observational studies
	D – Very low, e.g. case series or expert opinion
Factors influencing strength of evidence	
Methodological quality – poor planning and implementation increasing likelihood of bias is likely to decrease rating	
Importance of outcome – highly desirable outcomes are likely to increase rating	
Magnitude of treatment effect – RR > 2 with no plausible confounders is likely to increase rating	
Precision of estimate of treatment effect – highly precise results are likely to increase rating	
Inconsistency of results – multiple studies with inconsistent results is likely to decrease rating	
Directness of evidence – indirect evidence (e.g. different populations) is likely to decrease rating	
Risks associated with therapy – significant known risks or burden of therapy are likely to decrease rating	
Costs – significant costs associated with therapy are likely to decrease rating	

RCT: randomized control trial; RR: relative risk

As part of the various nursing considerations and strategies relevant for the prevention and treatment of sepsis, interventions in the field of preventing HAIs were reviewed and graded. An overview of the resulting recommendations, with their respective grades of evidence and rationale, is listed below.

Education

1. We recommend interactive, multifaceted, longitudinal educational programs and educational outreach to enhance guideline implementation. Traditional education approaches, such as incorporated passive education and information dissemination through conferences, web sites and didactic lectures, are often not effective (GRADE 1A).

2. We recommend educational initiatives to reduce healthcare-associated infection rates (GRADE 1C).

Rationale. Education is generally considered as a first step to increase awareness of a problem and as crucial for processes of change. A systematic review found that interactive, multifaceted, longitudinal educational programs and educational outreach enhance guideline implementation.[107] More specifically, a systematic review that investigated the effect of education on the reduction in infection rates concluded that the implementation of educational interventions may considerably reduce healthcare associated infections.[149]

Accountability

We suggest the promotion of a culture of patient safety and individual accountability (GRADE 2D).

Rationale. Recent trends have seen a transition from accepting healthcare-associated infection as an inevitable outcome of admission to the Intensive Care Unit (ICU)[54] towards personal accountability and a goal of zero tolerance in relation to hospital-acquired infections.[2, 3] A systematic review of 30 reports of nosocomial infection found that at least 20% could be preventable.[67] A major impediment to achieving zero tolerance towards hospital-acquired infection has been a lack of accountability of all levels of hospital staff.[2] This attitude is shifting, with recognition that hospital management, as well as every healthcare worker, is responsible and accountable for ensuring patient safety including infection prevention and control.[2, 3] Educating and empowering nurses to ensure infection control guidelines are followed by all staff has the potential to positively impact on hospital-acquired infections.[69, 74]

Surveillance of nosocomial infections

We recommend a continuous surveillance program for the detection of nosocomial infection (GRADE 1B).

Rationale. Local surveillance systems (eventually integrated in a national surveillance program) allow monitoring of nosocomial infection data and are therefore essential to guide and evaluate interventions to reduce infection rates. Surveillance systems combined with appropriate feedback contribute to reduced nosocomial infection risk.[150-155]

Hand hygiene

1. We recommend hand antisepsis, irrespective of the use of gloves, between caring for different patients or between different care activities for the same patient, immediately before and after each episode of direct patient contact, and after any activity or contact that potentially results in hands becoming contaminated (GRADE 1B).
2. We recommend hand antisepsis by means of an alcohol-based hand rub (GRADE 1A).
3. We recommend hand washing with soap and water when hands are visibly soiled (GRADE 1A).
4. We recommend the use of gloves when contact with blood or other potentially infectious materials, secretions, mucous membranes and non-intact skin could occur (GRADE 1D).

Rationale. Adequate hand antisepsis has proven to result in reduced infection rates.[9, 95] The use of alcohol-based hand rub is particularly effective; in contrast with hand washing, it kills susceptible bacteria more rapidly and to a greater extent, is less time consuming, and skin health is better preserved when moisturizers are added. Hand disinfection after glove removal is necessary because gloves may have imperceptible defects or may be torn during use, resulting in contamination of hands. Hand washing is necessary when hands are visibly dirty because alcohol-based hand rub is ineffective in the presence of organic material. However, after hand washing, the use of alcohol-based hand rub remains mandatory.[9, 95]

As a rule of thumb, a first step towards adequate hand hygiene consists of avoiding direct contamination of hands. The use of non-sterile, well-fitting gloves is recommended whenever the risk of contamination exists. Gloves must be changed between separate tasks on one patient (when going from a dirty/contaminated to a clean body site) and in between different patients. [9, 95, 156]

Site-specific considerations

Most healthcare associated infections in the ICU are related to the use of therapeutic devices. These include VAP, CVC-RI, SSI, and CAUTI.[157, 158] Recommendations for their prevention are outlined below.

Prevention of respiratory infections

The development of pneumonia in patients mechanically ventilated with an artificial airway may affect 10–48% of patients.[159-161] VAP is associated with a higher mortality rate, and

significantly longer ICU length of stay and hospital costs.[158, 160-162] However, VAP is often preventable, and application of practices such as education strategies[72, 163] and ventilator bundles[130, 164] have contributed to a reduction in VAP incidence. Strategies to prevent VAP should be considered in all patients with severe sepsis.[87]

1. We recommend head-of-bed elevation 30–45° for all critically ill and mechanically ventilated patients (GRADE 1B). Special attention should be given to manoeuvres in which it is difficult to achieve a 30° head-of-bed elevation, such as during bed bath or changing sheets. In such circumstances we recommend backrest elevation of at least 10° should be maintained.

Rationale. Aspiration of upper airway secretions is a common event even in normal healthy adults.[165] Semi-recumbent position in mechanically ventilated patients has been associated with lower levels of aspiration into the lower airways[166-168] and lower VAP incidence than the supine position.[169-171] In patients receiving enteral nutrition, head-of-bed elevation is especially effective in reducing the risk of VAP.[169] However, the feasibility of maintaining head-of-bed elevation in daily practice has been questioned by some authors.[172, 173] Van Nieuwenhoven et al.[173] achieved average head-of-bed elevation of only 28° despite a target of 45°, while Song et al.[172] achieved head-of-bed elevation >30° in 43.4% of patients.

2. We recommend the use of an endotracheal tube with subglottic secretion drainage in patients expected to require mechanical ventilation for more than 72 hours (GRADE 1A).

Rationale. Impaired gag reflex leads to pooling of secretions in the posterior part of the oropharynx,[174] with microaspiration of subglottic secretions leading to VAP. Subglottic secretion drainage is accomplished through use of a specially designed endotracheal or tracheotomy tube with a separate dorsal lumen that opens directly above the endotracheal tube cuff. Subglottic secretions drainage appears to be effective in preventing VAP (relative risk [RR] 0.51, 95% confidence interval [95% CI] 0.37–0.71) in patients expected to be mechanically ventilated for more than 72 hours.[175]

3. We suggest the use of a silver-coated endotracheal tube be considered (GRADE 2A).

Rationale. In multicenter randomized controlled trials, a silver-coated endotracheal tube was demonstrated to reduce bacterial airway colonization as well as VAP in patients intubated 24 hours or more.[176, 177] More studies that confirm the current findings are required.

4. We suggest the use of an endotracheal tube with a polyurethane cuff (GRADE 2B).

Rationale. In a single center randomized controlled trial, an endotracheal tube with a polyurethane cuff was shown to significantly reduce early onset post-operative pneumonia in cardiosurgical patients.[178] More studies that confirm this result are required.

5. We recommend endotracheal cuff pressure be maintained at least 20 cm H_2O, but not more than 30 cm H_2O (GRADE 1C).

Rationale. Inadequate cuff pressure is a risk factor for microaspiration of oropharyngeal secretions and subsequent pneumonia. One observational study among intubated patients not receiving antibiotic therapy showed that a persistent intracuff pressure below 20 cm H_2O was an independent predictor of VAP (RR 4.2, 95% CI 1.1–15.9).[179] Cuff pressure should be maintained at the lowest pressure above 20 cm H_2O that prevents cuff leak.

6. We suggest heat and moisture exchangers (HME) should be changed between patients, every 5–7 days, or as clinically indicated (GRADE 2C).

Rationale. Humidification of inspired air to prevent mucosal injury may be achieved by using a heated humidifier, a heated humidifier with a heated-wire circuit, or passively using a HME. There are insufficient data to demonstrate a benefit in VAP reduction for any humidification device.[180] No benefit in infection rates or functionality of ventilator circuits has been demonstrated when HMEs are changed every day compared to 5–7 days.[181, 182]

7. We recommend ventilator circuits should not be changed routinely, except between patients (GRADE 1B).

Rationale. There is no evidence that routine ventilator circuit changes can reduce the incidence of VAP.[159, 183] New ventilator circuits should be used for each patient, and circuit changes performed only if the circuit becomes visibly soiled or damaged.[87]

8. We recommend the aspiration of endotracheal secretions in response to clinical signs, i.e. visible or audible signs of respiratory secretions, respiratory deterioration or other changes in the patient's condition that may be due to respiratory secretions, in intubated patients (GRADE 1C).

Rationale. Critically ill patients mechanically ventilated via a tracheal tube frequently require removal of tracheobronchial and upper airway secretions due to increased mucus production and a decreased ability to clear secretions.[184, 185] Secretion removal may reduce infectious, respiratory and tube patency complications.[186-188]

Suctioning should only be performed when necessary, using the lowest possible suction pressure, take no longer than 15 seconds, use continuous rather than intermittent suctioning; the suction catheter should occlude less than half the lumen of the endotracheal tube and be inserted no further than the carina; hyperoxygenation should be provided before and after suctioning, and saline lavage should be avoided.[187-189]

The optimum frequency of endotracheal suctioning has not been clearly determined, but should be in response to clinical signs.[188] There is insufficient evidence to recommend the benefits of either an open or closed suctioning system.[189]

9. We recommend regular mouth care and oral cavity assessment be provided to all critically ill and intubated patients (GRADE 1C).

Rationale. Colonization of the oropharynx by pathogens is a potential risk factor for the development of VAP.[190-192] Critical illness contributes to changes in the oral flora, and an increase in gram-negative flora that includes more virulent organisms may occur.[193, 194] Providing regular oral care, incorporating oral cavity assessment, is an important part of providing comfort to the critically ill patient[195] and is also demonstrated to contribute to a decrease in VAP.[195-198] Assessment should include the condition of the teeth, gums, tongue, mucus membranes and lips, and barriers to mouth care delivery.[195] The use of a designated oral care protocol, in association with an education program for nurses in its importance in preventing VAP, can increase compliance and assessment of mouth care.[42]

10. We recommend the use of chlorhexidine-based antiseptic for oral care in intubated patients (GRADE 1A).

Rationale. Chlorhexidine is widely used and investigated in the oral care of intubated patients.[199-202] Chlorhexidine effectively decontaminates the oropharynx[203, 204] and its use in oral care has been proven to decrease dental plaque[205] and incidence of respiratory infections,[206] and substantially decrease the incidence of VAP.[207-209] The optimal concentration of chlorhexidine solution (0.12%, 0.2% or 2%) remains undetermined. The optimum frequency for oral care with chlorhexidine has not been demonstrated. In general, a frequency of 3–4 times daily is proposed.[199, 210, 211] The benefit of tooth brushing in critically ill patients as a component of oral care protocols has demonstrated efficacy but additional research is indicated.[197, 198] Tap water is not recommended for oral care in the critically ill.[195]

Prevention of catheter-related bloodstream infections (CR-BSI)

1. We recommend the implementation of a central line care bundle including staff education, creation of a catheter insertion cart, implementation of a checklist to ensure adherence to evidence based guidelines, empowering nurses to stop catheter insertion procedures when a guideline violation is observed, and daily assessment of possible catheter removal (GRADE 1B).

Rationale. A bundle approach to central venous catheter (CVC) insertion and care[69, 74, 118, 212] has proven to be effective in substantially reducing the rate of CR-BSI. Nurses play a key role in preventing CR-BSI infection through the activities outlined above.

2. We recommend the use of maximal sterile barriers during CVC insertion (GRADE 1A).

Rationale. During the CVC insertion procedure, all healthcare personnel involved must wear a mask, cap, sterile gown, and sterile gloves and the patient is to be covered with a large sterile drape.[88, 213-215] Use of maximal sterile barrier precautions during CVC insertion have led to reduced infection rates.[214, 216, 217]

3. We recommend the use of a chlorhexidine-based antiseptic for skin preparation before insertion and subsequent catheter care (GRADE 1A).

Rationale. As the risk of CR-BSI increases with the density of microorganisms at and around the insertion site,[9] site antisepsis is crucial in the prevention of infection. Aqueous chlorhexidine (2%) solution has consistently been found to be superior to both 10% povidone iodine and 70% alcohol for preventing CR-BSI.[218-220]

4. We suggest the replacement of administration sets every 96 hours (GRADE 2A), except when used for the administration of blood, blood products or lipids, in which case sets must be changed within 24 hours (GRADE 1A).

Rationale. A Cochrane systematic review found no increase in the risk for CR-BSI when the interval for administration set replacement was increased from 72 hours to 96 hours.[221] When a fluid that enhances microbial growth is infused (lipid emulsions, blood products) more frequent changes of administration sets are indicated because these products have been identified as independent risk factors for CR-BSI in both adults and neonates.[222-227]

5. We recommend the use of minocyclin-rifampin impregnated catheters (GRADE 1B).

Rationale. Studies have repeatedly demonstrated a significant reduction in CR-BSI with the use of impregnated CVCs in comparison with standard catheters;[228-231] this reduction in infection rates has been greatest with minocycline-rifampin coated CVCs when compared to other impregnated CVCs.[232] Minocycline-rifampin impregnated CVCs are approved for use in the pediatric population by the Food and Drug Administration (USA); however, studies have not been conducted in children.

Prevention of surgical site infections (SSI)

1. We recommend that antimicrobial prophylaxis be administered within one hour before incision to maximize tissue concentration. Two hours are allowed for the administration of vancomycin and fluoroquinolones (GRADE 1A).

Rationale. In 2003, the Surgical Infection Prevention Guideline Writers Workgroup meeting reviewed the various guidelines for antimicrobial prophylaxis in surgery.[233] On the basis of published evidence, the workgroup concluded that infusion of the first antimicrobial dose should begin within 60 minutes before incision, and when a fluoroquinolone or vancomycin is indicated the infusion should begin within 120 minutes before incision to prevent antibiotic-associated reactions.[89, 233]

2. We recommend that only hair that will interfere with the operation be removed, and that, if hair removal is necessary, it should be removed by using electric clippers (GRADE 1B).

Rationale. Although several authors have reported pre-operative hair removal is associated with increased SSI rates,[20, 234-236] a Cochrane systematic review compared a variety of hair removal methods (depilatory cream, razors, clippers) versus no hair removal and reported no difference in SSI rates among patients who had hair removal prior to surgery and those who did not.[236] The same review found that shaving led to statistically significantly more SSIs compared with clipping or depilatory cream.[236] The increased infection risk associated with the technique of shaving is attributed to the formation of microscopic cuts in the skin that later act as foci for bacteria.[20] Although the use of depilatories has been associated with a lower SSI risk than shaving or clipping[237, 238] they can produce hypersensitivity reactions.[238]

3. We recommend that blood glucose levels be controlled during the immediate post-operative period for patients undergoing cardiac surgery: controlled blood glucose level (lower than 200 mg/dL) on post-operative day 1 and post-operative day 2, with procedure day being post-operative day 0 (GRADE 1C).

Rationale. Increased glucose levels (>200 mg/dL) in the immediate post-operative period (≤48hrs) are associated with increased SSI risk.[239, 240] One study found that patients with blood glucose levels >300 mg/dL within 48hrs of surgery had over three times the likelihood of a wound infection.[241] Regular monitoring of glucose levels and timely administration of insulin and hyperglycemic agents is a direct nursing responsibility, therefore nursing education should stress the importance of glucose control in preventing SSI.

4. We recommend the identification and treatment of infections remote to the surgical site before elective surgery (GRADE 1B).

Rationale. Concurrent remote site infections are considered to increase SSI risk.[242-244] Therefore, whenever possible, all infections remote to the surgical site should be identified and treated before elective operation, and elective operations on patients with remote site infections should be postponed until the infection has resolved.[20]

Prevention of urinary tract infections (UTI)

1. We recommend that all attempts should be made to limit the duration of urinary catheterization (GRADE 1C).

Rationale. The urinary tract is the most prevalent source of nosocomial infection and there are several recommendations to prevent or reduce the incidence of UTI.[245] Duration of catheterization is the most important risk factor for developing UTI.[245] Post-operative urinary catheterization >2 days is associated with an increased likelihood of UTI and 30-day mortality, as well as a decreased likelihood of discharge to home.[246] Nurses should advocate for prompt removal of catheters[247] and discourage long-term catheterization, if possible.

2. We recommend that a sterile, continuously closed drainage system be maintained (GRADE 1A).

Rationale. Closed urinary drainage systems are pivotal in preventing UTI.[9, 247] The risk of infection reduces from 97% using open systems to 8–15% when sterile closed systems are

used.[248-250] Errors in maintaining sterile closed drainage and opening the closed drainage system have been well documented to predispose patients to infection.[248, 250-253]

3. We recommend regular perineal hygiene measures (GRADE 1C).

Rationale. Most episodes of UTI are caused by the patient's own flora.[245] Daily cleansing of the urethral meatus using soap and water or perineal cleanser is recommended.[247, 254]

4. We suggest the maintenance of unobstructed urine flow (GRADE 2C).

Rationale. Reflux of urine is associated with infection; therefore, drainage bags should be positioned below the level of the bladder at all times to prevent urine back-flow and unobstructed urine flow should be maintained.[9, 255, 256]

3.2. A systematic review and meta-analysis of randomised controlled trials

Based on the article: Labeau SO, Van de Vyver K, Brusselaers N, Vogelaers D, Blot SI. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. Lancet Infect Dis. 2011;11(11):845-854.

In case separate randomised controlled trials yield inconclusive evidence, a meta-analysis can help to limit uncertainty. Uncertainty is undeniably an important issue when entering the field of providing optimal oral care to intubated patients, regardless whether the outcome is patient comfort, oral health, prevention of VAP, or prevention of system diseases.[199] The lack of evidence pertains to various aspects of oral care, such as the best method, the best frequency, the best product and its best concentration.[199, 257]

Gaps in the evidence base of interventions hamper nursing practice.[258, 259] Aiming to contribute to determining best practice for oral care in intubated patients, we conducted a meta-analysis hypothesising that oral care with chlorhexidine or povidone-iodine reduces the occurrence of VAP in mechanically ventilated adults compared with absence of oral care or oral care with a placebo, saline 0.9%, or other active product.

Introduction

Ventilator-associated pneumonia is defined as pneumonia in people who have a device to continuously assist or control respiration through a tracheostomy or by endotracheal intubation within 48 h before the onset of infection, inclusive of the weaning period.[46]

Affecting 10–30% of mechanically ventilated patients, this type of pneumonia is one of the most frequent nosocomial infections in intensive care units.[49, 158] Depending on the casemix, disease severity, microorganisms involved, and adequacy of anti-infective management, the attributable mortality (mortality in exposed patients in excess to mortality in matched unexposed patients) can exceed 50%.[260] Moreover, ventilator-associated pneumonia is an important cause of morbidity, increased use of health-care resources, and excess cost.[158] As such, prevention of this disease is a priority in quality improvement programmes in intensive care units[85, 261] and plenty of efforts have been taken to elucidate the effect of distinct preventive measures.[164, 262, 263]

The most important mechanism for development of ventilator-associated pneumonia is aspiration of colonised oropharyngeal secretions into the lower respiratory tract.[264] Oral bacterial colonisation results from accumulation of debris in the oral cavity. Adequate salivary flow is an important factor for maintenance of oral health through its antimicrobial, lubricating, and buffering properties. In intubated patients, however, a constantly open mouth and the use of drugs such as antihypertensives, anticholinergics, antipsychotics, and diuretics predispose for xerostomia and subsequent reduction in salivary immune factors. Additionally, an endotracheal tube can hamper thorough inspection of the oral cavity and limit access for oral care. [199, 211] Reduction of the number of oral microorganisms might hold a potential for prevention of ventilator-associated pneumonia. [205, 265] Both chlorhexidine and povidone-iodine have been proposed as powerful antiseptic drugs against oral bacteria, but studies aiming to determine the most effective product, its optimum concentration, and frequency of use have yielded inconclusive results. We did a systematic review and subsequent meta-analysis postulating that oral care with chlorhexidine or povidone-iodine reduced the occurrence of ventilator-associated pneumonia in mechanically ventilated adults compared with absence of oral care or oral care with a placebo, saline 0.9%, or another active product.

Methods

Search strategy

Our systemic search for relevant publications included the electronic databases PubMed, CINAHL, Web of Science, and The Cochrane Central Register of Controlled Trials (CENTRAL).

We searched combinations of the keywords “oral care”, “oral health”, “oral hygiene”, “oral decontamination”, “antiseptics”, “intubation”, “(mechanical) ventilation”, “ventilator-associated pneumonia”, “prevention”, “reduction”, “pneumonia”, “respiratory (tract) infection”, “chlorhexidine”, “iodine”, “betadine”, “povidone”, and “nosocomial pneumonia”. We included articles in English, French, or Dutch published from January, 1975 to February, 2011. We identified unpublished studies in conference abstracts or in registers of clinical trials (ClinicalTrials.gov and Current Controlled trials). We also consulted bibliographies of relevant articles, science citation index, and Google Scholar.

Study selection

We narrowed the list of publications obtained to studies meeting our predetermined inclusion criteria. Thereby, we included only randomised controlled trials of mechanically ventilated adult patients receiving oral care with chlorhexidine or povidone-iodine. We excluded studies in which antibiotics were used as experimental intervention for oral decontamination. We included standard oral care, use of a placebo, or another product for oral care as control interventions. We retained only studies reporting rates of ventilator-associated pneumonia as outcome. Two investigators (Nele Brusselaers and Katrien Van de Vyver) did a first broad selection based on study title, under close supervision of the principal investigator (Stijn Blot) who is a content expert. To allow further narrowing, four independent reviewers (Katrien Van de Vyver, Stijn Blot, Sonia Labeau, Nele Brusselaers) screened the selected abstracts, each masked to the results of the others’ selection. Mostly, all reviewers decided unanimously. In one case of disagreement, assessment of eligibility was done by mutual consideration.

Data extraction

Categories of extracted data included author and year of publication, settings and study populations, inclusion and exclusion criteria, definitions and diagnosis of ventilator-associated pneumonia, intervention in the study and the control group, and prevalence of the disease. The concentration of the antiseptic used and the application method were also extracted from the studies if available. Prevalence was registered as the proportion of patients with ventilator-associated pneumonia to the total number of patients, in both study and control groups. When important data were missing, the author was contacted.

Secondary outcome variables were extracted for the systematic review, but not included in the meta-analysis.

Quality assessment

The quality of the included randomised trials was assessed by two reviewers (Nele Brusselaers and Katrien Van de Vyver) with a validated checklist of the Dutch Cochrane Centre (Addendum 4, Dutch version, English version not available), and subsequently appraised by another reviewer (Sonia Labeau).[266] This checklist consists of three major parts: (a) assessment of the validity; (b) assessment of the study results; and (c) assessment of the applicability (in the Dutch healthcare system).

Criteria for validity assessment included the use of (blinded) randomisation and masking of patient, practitioner, or assessor. Additionally, the comparability of the groups at baseline, loss-to-follow-up, intention-to-treat analysis, and comparability of treatment were evaluated. Table 2a provides an overview of the validity indicators of each study according to the checklist. Table 2b relates to the assessment of the study results. The part of the checklist concerning the applicability (in the Dutch healthcare system) was not used as this did not yield additional useful information concerning the methodological quality of the studies included.

An additional quality check included assessment of the sample size, definition of inclusion and exclusion criteria, and clear definition of outcomes (Table 3).

Statistical analysis

We did a random-effects meta-analysis using Review Manager 5.0 (Cochrane Collaboration, 2008) following the Mantel-Haenszel model to obtain relative risks (RR) and 95% CIs. We assessed clinical heterogeneity by comparing protocol, populations, and methodology of the studies included. We assessed statistical heterogeneity using the I^2 statistic that measures the degree of inconsistency across studies; it results in a 0–100% range quantifying the proportion of variation in the effect, which is due to inter-study variation. We predefined heterogeneity ($I^2 \leq 25\%$ for low, $25\% < I^2 < 50\%$ for moderate, and $I^2 \geq 50\%$ for high). We constructed a funnel plot to assess publication bias and did sensitivity analysis by different subgroup analyses. A p value of less than 0.05 was used to denote statistical significance.

Results

Our broad search strategy yielded 1720 abstracts (873 in PubMed, 502 in Web of Science, 78 in CINAHL, and 267 in CENTRAL). After elimination of identical publications and studies that did not meet inclusion criteria, 13[205, 206, 209, 265, 267-275] studies were selected. Scanning of reference lists yielded one additional study.[276] As a result, 14 studies published in English between January, 1996 and February, 2011 consisting of 2481 patients were included in the systematic review (Figure 1). Construction of funnel plot did not show publication bias (Figure 2).

Sample sizes varied considerably (Table 3). With regard to interventions, Seguin and colleagues[267] randomly assigned patients in the intervention group to receive oral care with either povidone-iodine or saline. For the present meta-analysis, the patients treated with povidone-iodine were considered the intervention group, and were compared with the joint saline and standard regimen groups (controls). Also, a study group combining the use of chlorhexidine and colistin (Koeman and colleagues)[271] was excluded from the present analysis. Scannapieco and colleagues[275] randomly assigned their study patients to (1) a control group with placebo administration twice daily; (2) an experimental group with 0.12% chlorhexidine once daily and placebo application once daily; and (3) an additional experimental group with 0.12% chlorhexidine administration twice daily. For the present analysis, both groups in which patients were given chlorhexidine 0.12% were considered as experimental groups.

Interventions varied considerably between studies. Teeth were brushed before application of antiseptics,[209, 268, 276] oral rinse with 15 mL chlorhexidine was applied with a sponge swab for 30 s,[206, 270] chlorhexidine gel was given after rinse of the mouth and oropharyngeal aspiration,[205, 269] chlorhexidine was used as a spray or swab, [265] or multiple interventions were combined.[209] Koeman and colleagues[271] applied chlorhexidine paste 2 cm bilaterally in the mouth after removal of remnants of the previous dose with a gauze moistened with saline 0.9%. In the study by Panchabhai and colleagues,[274] application of chlorhexidine 0.12% was preceded by oral and pharyngeal suction of pooled secretions, and by swabbing of the oral cavity, teeth, palate, buccal spaces, posterior pharyngeal wall, and hypopharynx with normal saline solution. Nurses trained in the study protocol gave 15 mL chlorhexidine 0.12% after mechanical cleaning of the mouth.[273] Chlorhexidine was also

Table 2a: Validity assessment of the studies included

Author (year)	Randomised Y/N/NA	Consealed randomisation Y/N/NA	Patients blinded Y/N/NA	Practitioner blinded Y/N/NA	Assessor blinded Y/N/NA	Groups comparable at baseline Y/NC/NNC/NA	Follow-up Y/N/NA	Analysed in group of randomisation Y/N/NA	Groups equally treated Y/N/NA	Inter-mediate assessment S/D/I
De Riso et al. (1996)[17]	Y	N	Y	Y	Y	Y	Y	Y	Y	S
Fourrier et al. (2000)[9]	Y	N	N	N	Y	Y	Y	Y	Y	S
Houston et al. (2002)[19]	Y	NA	N	N	NA	Y	Y	Y	NA	S
Chua et al. (2004)[25]	Y	Y	N	Y	Y	Y	Y	Y	Y	S
Grap et al. (2004)[10]	Y	N	NA	NA	N	Y	N**	Y	Y	D
Macnaughton et al. (2004)[20]	Y	N	Y	Y	Y	Y	Y	NA	NA	S
Fourrier et al. (2005)[18]	Y	N	Y	Y	Y	Y	Y	Y	Y	S
Bopp et al. (2006)[16]	Y	NA	N	N	NA	NNC	Y	y	NA	I
Koeman et al. (2006)[3]	Y	N	Y	Y	Y	Y	Y	Y	Y	S
Seguin et al. (2006)[15]	Y	N	Y	N	N	Y	Y	Y	Y	S
Tantipong et al. (2008)[21]	Y	NA	NA	NA	NA	Y	Y	Y	Y	S
Scannapieco et al. (2009)[24]	Y	Y	Y	Y	Y	Y	Y	Y	Y	S
Panchabhai et al. (2009)[23]	Y	Y	N	N	Y	Y	Y	Y	Y	S
Bellissimo-Roderigues et al. (2009)[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	S

Y: Yes; N: No; NA: Information Not Available; NC: No, but corrected for in analysis; NNC: No and not corrected for in analysis; S: Sufficiently valid and applicable; D: Doubtful; I: Insufficiently valid and applicable; **: No, but selective loss-to-follow-up sufficiently excluded

Table 2b: Results assessment of the studies included

Author (year)	Outcome*	Follow-up					p(I) Event	p(C) Event	ARR	NNT	RR	RRR
			Group	**Event**	**No event**	**Total**						
De Riso et al. (1996)[17]	VAP/no VAP	ICU discharge or death	**Intervention**	3	167	170	0.0176	0.05	-0.032	31.25	0.352	0.648
			Control	9	17	180						
			Group	**Event**	**No event**	**Total**						
Fourrier et al. (2000)[9]	VAP/no VAP	ICU discharge	**Intervention**	5	25	30	0.167	0.6	-0.433	2.31	0.278	0.722
			Control	18	12	30						
			Group	**Event**	**No event**	**Total**						
Houston et al. (2002)[19]	VAP/no VAP	10 days post-operative, extubation, tracheostomy, VAP diagnosis, or death	**Intervention**	4	266	270	0.015	0.031	-0.016	62.5	0.484	0.516
			Control	9	282	291						
			Group	**Event**	**No event**	**Total**						
Chua et al. (2004)[25]	VAP/no VAP	extubation, death, VAP diagnosis	**Intervention**	6	16	22	0.273	0.4	-0.127	7.874	0.682	0.318
			Control	8	12	20						
			Group	**Event**	**No event**	**Total**						
Grap et al. (2004)[10]	VAP/no VAP	extubation or 72 hours after inclusion	**Intervention**	4	3	7	0.571	0.6	-0.029	34.483	0.951	0.049
			Control	3	2	5						
			Group	**Event**	**No event**	**Total**						
Macnaughton et al. (2004)[20]	VAP/no VAP	extubation	**Intervention**	32	59	91	0.352	0.318	0.034	29.41	1.107	0.107
			Control	28	60	88						
			Group	**Event**	**No event**	**Total**						
Fourrier et al. (2005)[18]	VAP/no VAP	28 days, ICU discharge, or death	**Intervention**	13	101	114	0.114	0.105	0.009	111.1	1.086	0.086
			Control	12	102	114						
			Group	**Event**	**No event**	**Total**						
Bopp et al. (2006)[16]	VAP/no VAP	ICU discharge	**Intervention**	0	2	2	0	0.33	0	/	/	/
			Control	1	2	3						

Koeman et al. (2006)[3]	VAP/no VAP	extubation, death, VAP diagnosis, or withdrawal consent	**Group**	**Event**	**No event**	**Total**	0.102	0.177	-0.075	13.33	0.576	0.424
			Intervention	13	114	127						
			Control	23	107	130						
Seguin et al. (2006)[15]	VAP/no VAP	ICU discharge, or death	**Group**	**Event**	**No event**	**Total**	0.083	0.419	0.336	2.976	0.198	0.802
			Intervention	3	33	36						
			Control	13	18	31						
Tantipong et al. (2008)[21]	VAP/no VAP	extubation	**Group**	**Event**	**No event**	**Total**	0.049	0.114	0.065	15.38	0.43	0.57
			Intervention	5	97	102						
			Control	12	93	105						
Scannapieco et al. (2009)[24]	VAP/no VAP	21 days, extubation, ICU discharge, or death	**Group**	**Event**	**No event**	**Total**	0.121	0.203	-0.082	12.19	0.596	0.404
			Intervention	14	102	116						
			Control	12	47	59						
Panchabhai et al. (2009)[23]	VAP/no VAP	ICU discharge or death	**Group**	**Event**	**No event**	**Total**	0.159	0.181	-0.022	45.45	0.878	0.122
			Intervention	14	74	88						
			Control	15	68	83						
Bellissimo-Roderigues et al. (2009)[22]	VAP/no VAP	48 hours after ICU discharge	**Group**	**Event**	**No event**	**Total**	0.25	0.246	0.004	250	0.016	0.984
			Intervention	16	48	64						
			Control	17	52	69						

*: VAP incidence, expressed as the number of VAPs which developed in the intervention and control groups was the primary outcome of the meta-analysis. Other outcome measure, as mentioned by some of the authors, were not taken into account

p(I) Event: chance of event in Intervention group

p(C) Event: chance of event in Control group

ARR: Absolute Risk Reduction

NNT: Number Needed to Treat

RR: Relative Risk

RRR: Relative Risk Reduction

VAP: Ventilator-Associated Pneumonia

ICU: Intensive Care Unit

Table 3: Study characteristics of subpopulations included

Author (year)		Inclusion	Exclusion	Diagnose VAP	Intervention	Control	Blinded Y(es)/N(o)
De Riso et al. (1996)[17]	Cardiothoracic (open heart surgery)	CABG**,** valve surgery, septal surgery, cardiac tumor excision, or combinations	Intraoperative death, preoperative infection or intubation, pregnancy, heart and lung transplant recipients, hypersensitivity to CHX	New or progressing pulmonary infiltrate, fever, leukocytosis, and purulent tracheobronchial secretions	CHX 0.12% 15ml oral rinse 2x/d, start pre-operatively and continue postoperatively until discharge from ICU or death (n=173)	Placebo (n=180)	Y
Fourrier et al. (2000)[9]	Medico-surgical ICU	Age >18 years, medical condition suggesting ICU stay ≥ 5 days, mechanically ventilated by orotracheal or nasotracheal intubation or tracheostomy	Edentulous patients	Temperature>38°C or <36°C, infiltrates on chest radiographs, leukocytosis (>10.10³/mm³) or leukopenia (>3.10³/mm³), positive culture from tracheal aspirate and/or positive culture of BAL	CHX 0.2% gel 3x/d during ICU stay (n=30)	Standard oral care: mouth rinsing with bicarbonate isotonic serum, oropharyngeal sterile application 4x/d (n=30)	Y
Houston et al. (2002)[19]	Cardiothoracic (open heart surgery)	Patients after CABG and/or valve surgery requiring cardiopulmonary bypass	Intraoperative death, pregnancy, preoperative documented respiratory infection	New or progressing pulmonary infiltrate, fever, leukocytosis, positive microbial culture results	CHX 0.12% 15ml oral rinse 2x/d, start pre-operatively until 10 days postoperative or until extubation, tracheostomy, death, or diagnosis pneumonia (n=270)	Listerine® (phenolic mixture) 15 ml oral rinse 2x/d (n=291)	N
Chua et al. (2004)[25]	Medical, surgical, neurological, neurosurgical & central ICU	Mechanically ventilated adults (> 18 years), seen within 24 hours of intubation	Nosocomial pneumonia, hyperthyroidism, hypersensitivity to povidone-iodine	As defined by Centers of Disease Control and Prevention[1]	PVP-I 1% 3x/d + teeth cleaning 1x/d (n=22)	Placebo + teeth cleaning 1x/d (n=20)	Y

Grap et al. (2004)[10]	Surgical trauma ICU, neuroscience ICU, emergency department	Age > 18 years, endotracheally intubated & mechanically ventilated	Edentulous patients	Clinical Pulmonary Infection Score > 6	CHX 0.12% 2ml single application (n=7)	Standard oral care (n=5)	Y
Macnaughton et al. (2004)[20]	Mixed surgical-medical ICU	Patients requiring ventilatory support for at least 48 hours	Treatment for infections at admission of ICU, hypersensitivity to CHX	Leukocytosis, fever > 38°C, deterioration in oxygenation/chest signs, new consolidation on chest radiograph, significant bacterial growth on BAL, CPIS > 6	CHX 0.2% 2x/d (n=91)	Placebo (n=88)	Y
Fourrier et al. (2005)[18]	ICUs	Age>18 years, medical condition suggesting ICU stay ≥ 5 days, mechanically ventilated by oro- or nasotracheal intubation	Patients with tracheostomy, or hospitalised for > 48 hours before ICU admission, edentulous patients, facial trauma, postsurgical and requiring specific oropharyngeal care, allergy to CHX	Temperature>38°C or <36°C, new infiltrates on chest radiographs, leukocytosis (>10.10^3/mm^3) or leukopenia (>3.10^3/mm^3), positive quantitative culture from tracheal aspirate and/or BAL	CHX 0.2% gel 3x/d until day 28; toothbrushing was not allowed (n=114)	Placebo (n=114)	Y
Bopp et al. (2006)[16]	Critical care unit	Orally or nasally intubated patients	Patients on metronidazole, allergy to CHX, sensitivity to alcohol, risk for infective endocarditis, history or presence of various comorbidities; and /or admitted to hospital with pneumonia and subsequently intubated	VAP was diagnosed by a physician, criteria are not specified	CHX 0.12% 2x/d until extubation, toothbrushing with CHX (n=2)	Standard oral care 2x/d with foam swab, hydrogen peroxide and oral lubricant (n=3)	N

Koeman et al. (2006)[3]	Mixed and surgical ICUs	Age > 18 years, requiring mechanical ventilation for ≥ 48 hours	Pre-admission immunocompromised status, pregnancy, physical condition not allowing oral application of study medication	New, persistant or progressive infiltrate on chest radiograph + at least 3 of 4 criteria: fever > 38°C or < 35.5°C, leukocytosis (>10.10³/mm³) or leukopenia (>3.10³/mm³), purulent aspect of tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% paste 4x/d until diagnosis VAP, death, extubation, or withdrawal of consent (n=127)	Placebo (n=130)	Y
Seguin et al. (2006)[15]	Surgical ICU	Adult patients > 18 years, severe closed head trauma, expected to need mechanical ventilation for > 2 days	Admitted to ICU > 12 hours after initial trauma with facial, thoracic, abdominal, or spinal injuries, reaction to iodine, respiratory disease, infiltrates on chest radiograph, need for curative antibiotics	New, pulmonary infiltrate on chest radiograph + 2 of the following: fever > 38°C or < 36°C, purulent endotracheal aspirate, leukocytosis (>10.10³/mm³) or leukopenia (>3.10³/mm³), bacterologic culture growth BAL	Povidone-iodine 10% 6x/d (n=36)	Standard care without instillation but with aspiration of secretions 6x/d (31) OR nasopharynx and oropharynx rinsing with 60 mL of saline solution 6x/d (n=31)	N
Tantipong et al. (2008)[21]	ICU	Adult patients > 18 years, mechanically ventilated	Pneumonia, allergy to CHX	New, persistant or progressive infiltrate on chest radiograph + at least 3 of 4 criteria: fever > 38°C or < 35.5°C, leukocytosis (>10.10³/mm³) or leukopenia (>3.10³/mm³), purulent tracheal aspirate, positive semiquantitative culture from tracheal aspirate	CHX 2% 15 ml solution 4x/d with toothbrushing (n=102)	Saline, with the same oral care procedure (n=105)	N

Scannapieco et al. (2009)[24]	Trauma ICU	Adult patients > 18 years, intubated and mechanically ventilated within 48 hours of admission	Witnessed aspiration; confirmed diagnosis of post-obstructive pneumonia; known hypersensitivity to CHX; absence of consent; diagnosed thrombocytopenia (platelet count less than 40 and/or a INR above 2, or other coagulopathy); do not intubate order; pregnancy; legal incarceration; transfer from another ICU; oral mucositis; immunosuppression (either-HIV or drug induced; and re-admission to the ICU	Upon suspicion of pneumonia, lung secretions analysis by Blind Quantitative Bronchoalveolar Lavage (bqBAL) using a mini-BAL technique with $>10^4$CFU/ml of a target PRP in bqBAL fluid or a positive pleural fluid culture in the absence of previous pleural instrumentation considered as positive evidence for diagnosis of pneumonia.	CHX 0.12% 1x/day plus placebo (n=58) OR CHX 0.12% 2x/day (n=58)	Placebo 2x/day (n=59)	Y (double-blind)
Panchabhai et al. (2009)[23]	Mixed ICU	All patients admitted to the ICU during the 8-month study period	Pregnancy; pneumonia on hospital admission; patients in whom oral care was contraindicated or with history of allergy to CHX	Nosocomial pneumonia was defined by 2 independent, blinded reviewers: development of new persistent alveolar infiltrates on chest radiograph; >38°C; leukocytosis (>12.10³ WBCs/µL), and purulent sputum developing >48 hours after ICU admission with worsening of hypoxemia on arterial blood gas analysis. All parameters were essential for the diagnosis.	10 ml CHX 0.2% 2x/day (n=88)	10 ml 0.01% potassium permanganate 2x/day (n=83)	N

				Semiquantitative cultures obtained by the protected nonbronchoscopic mini-BAL technique were considered positive with >10^3 CFU/ml. A positive culture was not essential for the diagnosis of pneumonia.			
Bellissimo-Roderigues et al. (2009)[22]	Mixed ICU	All patients admitted to the ICU with a prospective length of stay > 48 hours, regardless of whether they received mechanical ventilation.	Previous CHX hypersensitivity; pregnancy; formal indication for CHX use, or prescription of another oral topical medication.	As defined by Centers of Disease Control and Prevention[1]	CHX 0.12% 15ml after mechanical cleaning 3x/day (n=64)	Placebo 15ml after mechanical cleaning 3x/day (n=69)	Y (double-blind)

CHX = chlorhexidine
ICU = Intensive Care Unit
PVP-I = povidone-iodine
CABG = Coronary Artery Bypass Grafting
VAP = Ventilator-Associated Pneumonia
BAL = BronchoAlveolar Lavage
CFU = Colony Forming Units
PRP = potential respiratory bacterial pathogen

applied with a rinse-saturated oral foam applicator.[275] Seguin and colleagues[267] rinsed the nasopharynx and oropharynx with 20 mL povidone-iodine 10% reconstituted in a 60 mL solution with sterile water, followed by aspiration of oropharyngeal secretions. Chua and colleagues[276] rinsed the oropharyngeal area with cotton pledgets soaked in 15–20 mL sterile water, then swabbed the entire oropharyngeal mucosa and part of the endotracheal tube with cotton pledgets soaked in povidone-iodine 1%. Chlorhexidine was used at concentrations of 0.12%,[206, 265, 268, 270, 273, 275] 0.2%,[205, 269, 272, 274] and 2%,[271] and povidone-iodine at 1%[276] and 10%.[267] Frequency of antiseptic application varied from once[265, 275] or twice a day,[206, 268, 270, 272, 274, 275] over three[205, 269, 273, 276] and four[209, 271] to six times a day.[267]

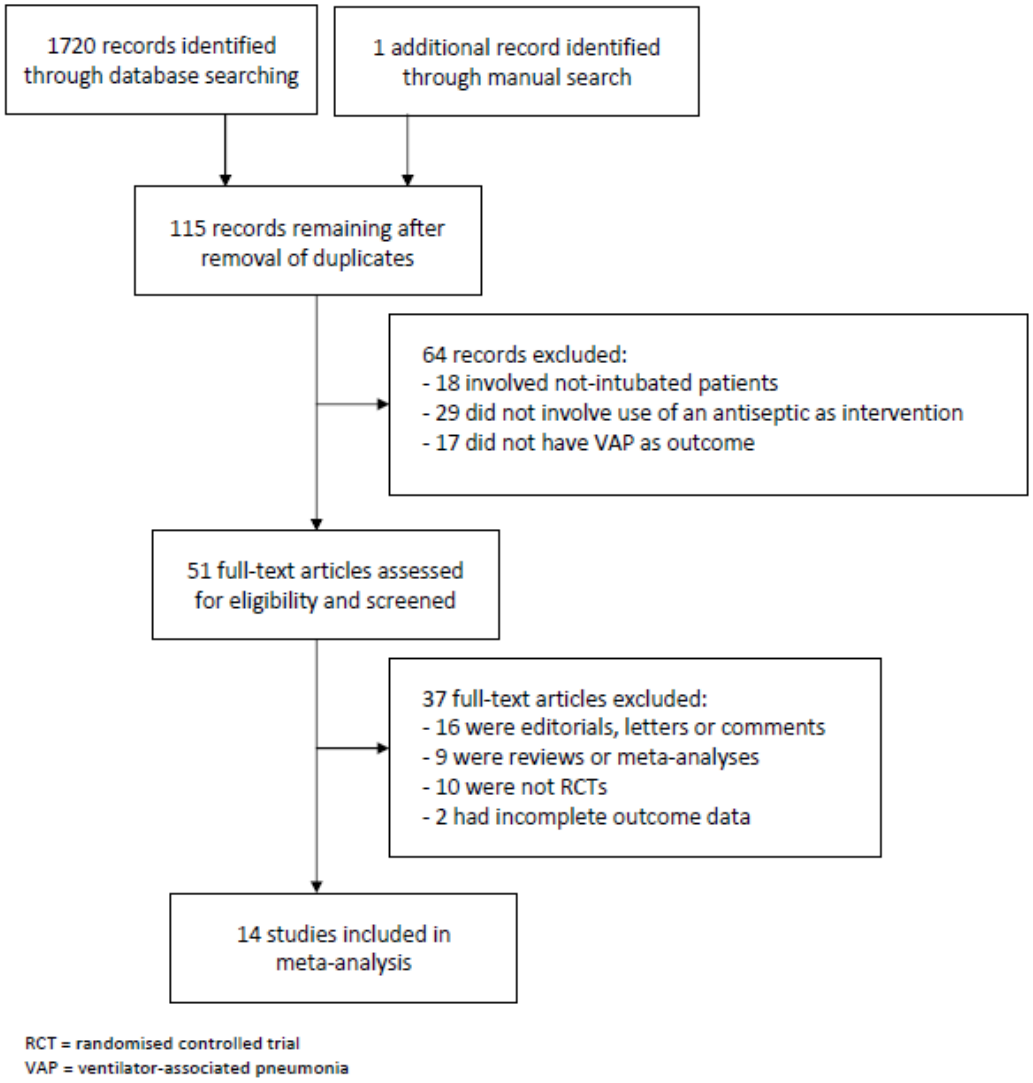

Figure 1: Summary of literature search and study selection; VAP = ventilator-associated pneumonia

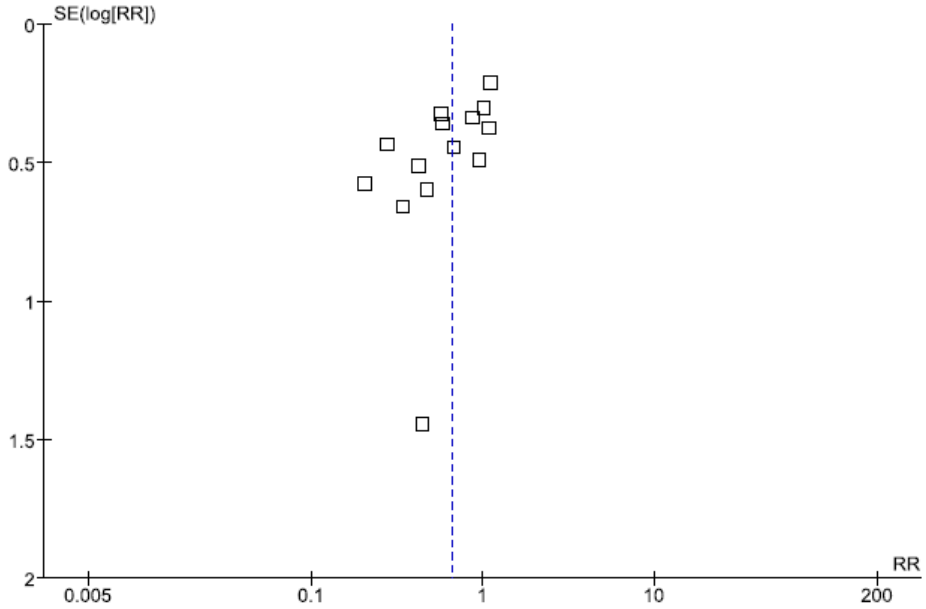

Figure 2: Funnel plot of the included studies

Chlorhexidine was applied as oral rinse, foam, gel, or paste and povidone-iodine as oral rinse only. Duration of oral care varied greatly between studies and was not always reported.

In the chlorhexidine studies, patients in the control group were given a placebo (n=640),[206, 269, 271-273, 275] standard oral care (n=38),[205, 265, 268] saline 0.9% (n=105),[209] potassium permanganate 0.01% (n=82),[274] or the phenolic oral rinse Listerine (Johnson & Johnson Limited; n=291; Table 3).[270] In the povidone-iodine studies, patients in the control group were given a placebo (n=20),[276] saline,[267] or 'standard' oral care (n=62).[267] The definition of standard oral care varied noticeably between trials.

Age older than 18 years was specified as inclusion criterion in eight studies (Table 3).[205, 209, 265, 267, 269, 271, 275, 276] All others[206, 268, 270, 272-274] also included adults only but did not specify the lower age limit for inclusion. Exclusion criteria varied widely. With regard to diagnostic criteria, Grap and colleagues[265] used the Clinical Pulmonary Infection Score (CPIS) for definition of ventilator-associated pneumonia. The other studies applied the US Centers for Disease Control and Prevention (CDC) definitions for nosocomial pneumonia[206, 270, 273, 276] or similar definitions.[205, 209, 267, 269, 271, 272] Bopp and colleagues[268] reported no diagnostic criteria. Nosocomial pneumonia was defined by two independent, masked reviewers in the study by Panchabhai and colleagues.[274] Scannapieco and colleagues[275] based their diagnosis on microbiological assessment of lung secretions.

Two studies[206, 270] done in cardiothoracic intensive-care units reported antibiotic administration perioperatively and until 48 h postoperatively. Stress ulcer prophylaxis,[206, 274] semirecumbent body position with head of bed elevation of 30°,[209, 267, 271, 274] daily assessment for readiness for extubation,[274] deep vein thromboprophylaxis, [274] and regular emptying of condensate from ventilator tubing[274] were also reported. Although, even if not mentioned, these are components of standard care and, as such, were probably applied as part of routine practice. In a medico-surgical intensive-care unit, Fourrier and colleagues[205] reported prevalences of ventilator-associated pneumonia of 17% (five of 30 patients) in the interventional group and 60% (18 of 30 patients) in the control group, accounting for 10.7 and 32.3 episodes of ventilator-associated pneumonia per 1000 ventilator-days, respectively ($p<0.05$; relative risk [RR] reduction 53%). In the study by Koeman and colleagues[271] 52 patients were diagnosed with ventilator-associated pneumonia (13 [10%] of 127 patients in the chlorhexidine group and 23 [18%] of 130 in the control group; the remaining 16 [13%] patients were given a combination of chlorhexidine 2% and colistin 2% as part of an intervention group. This group was not included in our study. Tantipong and colleagues[209] reported five (4.9%) of 102 patients with the disease in the chlorhexidine group and 12 (11.4%) of 105 patients in the control group (RR 0.43, 95% CI 0.16–1.17; $p=0.08$) with a mean number of seven cases per 1000 ventilator-days in the intervention group and 21 per 1000 ventilator-days in the control group ($p=0.04$). In the povidone-iodine study by Seguin and colleagues[267] a significant decrease ($p=0.001$) in the rate of pneumonia in surgical patients was shown in the intervention group (three [8%] of 36 patients [95% CI 0–17] versus 12 [39%] of 31 patients [95% CI 22–56] in the control group [$p=0.003$] and 13 [42%] of 31 patients [95% CI 25–59] in the saline and the standard regimen groups [$p=0.001$]).[267] In the povidone-iodine study by Chua and colleagues[276] in a mixed intensive-care unit, the rates of pneumonia did not differ between both groups ($p=0.58$).

We did a meta-analysis of all 14 retrieved studies[205, 206, 209, 265, 267-276] to assess the pooled effect of oral care with topical chlorhexidine or povidone-iodine on the occurrence of ventilator-associated pneumonia. This analysis showed an important reduction of the disease ($p=0.004$; Figure 3), with a moderate statistical heterogeneity. Subgroup analysis based on type of antiseptic showed a significant reduction in cases of ventilator-associated pneumonia in the chlorhexidine studies, but the effect resulting from povidone-iodine

remains unclear (Figure 3). The povidone-iodine subanalysis was based on fewer studies, and also showed a larger heterogeneity and broader CIs (Figure 3).

To determine the most effective chlorhexidine concentration, subgroup analyses included chlorhexidine 2%,[209, 271] 0.2%[205, 269, 272, 274] and 0.12%.[206, 265, 268, 270, 273, 275] Chlorhexidine 2% was to be associated with a significant risk reduction with a low heterogeneity (Figure 4). This protective effect of chlorhexidine was less strong at lower concentrations, with an RR of 0.79 for chlorhexidine 0.2% and 0.73 for chlorhexidine 0.12%, and with broad 95% CIs enclosing RR 1 (nil effect; Figure 4). Results from the studies assessing the use of chlorhexidine 0.12%, however, showed true homogeneity.

Given their specific profile in terms of infection control, the use of chlorhexidine in all concentrations was compared between cardiosurgical, [206, 270] mixed, [205, 209, 265, 268, 269, 271-274] and surgical or trauma intensive-care unit populations.[267, 275] This analysis showed a significant risk reduction associated with the intervention in cardiosurgical patients (Figure 5). The two cardiosurgical studies[206, 270] were homogeneous. In both groups of non-cardiosurgical patients, the risk reduction was not significant (Figure 5). Subanalyses considering blinded[205, 206, 265, 269, 271-273, 275, 276] studies showed a RR of 0.73 (95% CI 0.54–1.00) and those considering non-blinded[209, 267, 268, 270, 274] studies a RR of 0.50 (95% CI 0.29–0.87; data not shown).

Discussion

This meta-analysis of 14 randomised trials provides strong evidence that oral care with chlorhexidine or povidone-iodine effectively reduces rates of ventilator-associated pneumonia when compared with oral care without these antiseptics. This effect was most prominent for chlorhexidine 2%. For chlorhexidine 0.12%, which is currently the recommended dosage by the CDC for cardiosurgical patients,[18] the risk reduction was not significant. With regard to povidone-iodine application, only two rather small studies with higher statistical heterogeneity could be assessed. Although the evidence was not statistically convincing, the risk reduction associated with povidone-iodine use was substantial. As such, povidone-iodine might become a worthy alternative for chlorhexidine, which is currently regarded as the gold standard,[277] without the disadvantage of brown-staining teeth in chronic use.[278] Larger and standardised comparative studies are necessary

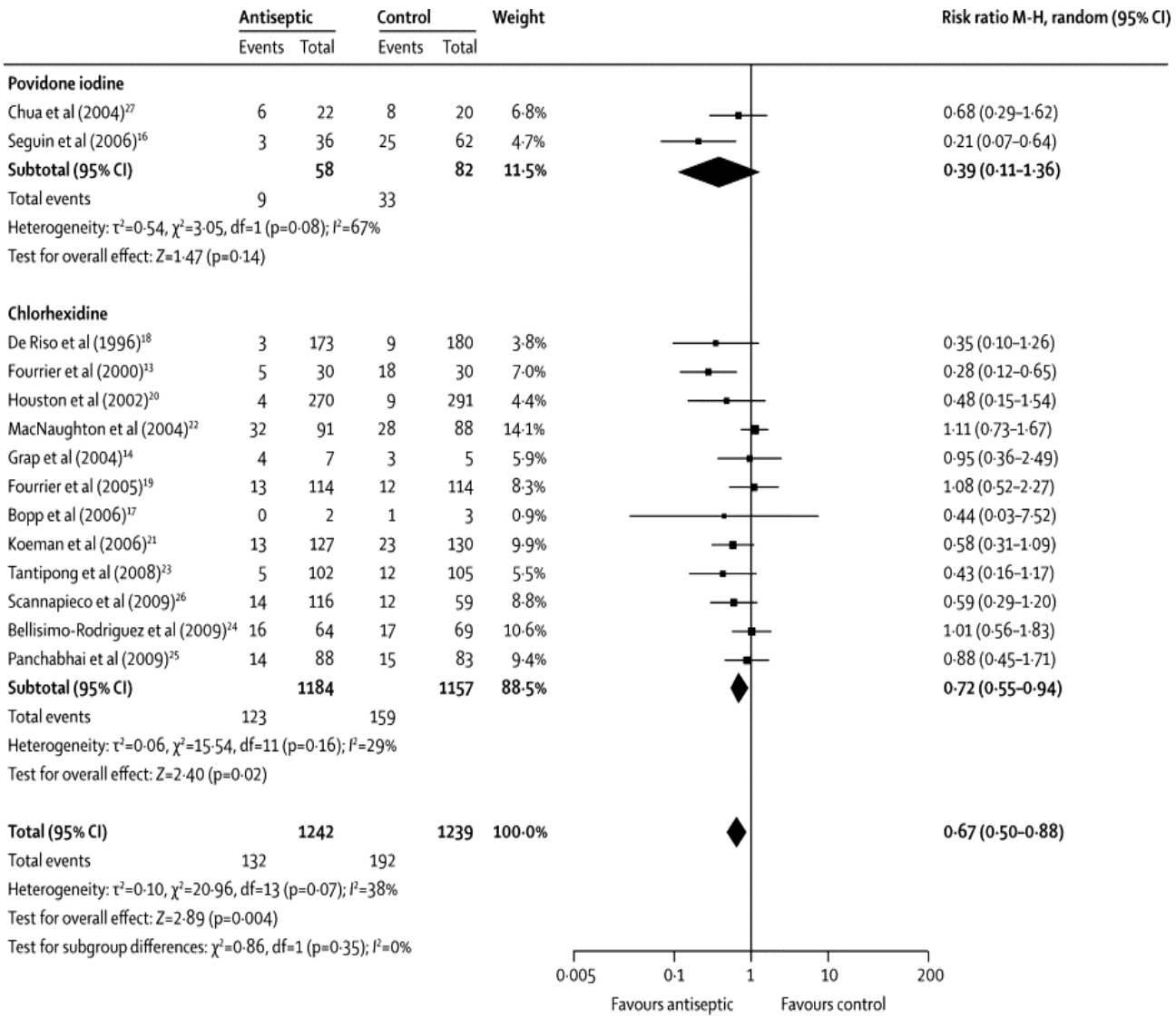

Figure 3: Overall effect of oral antiseptic use on the prevalence of ventilator-associated pneumonia, and subanalysis of chlorhexidine versus povidone-iodine use; M-H=Mantel-Haenszel test

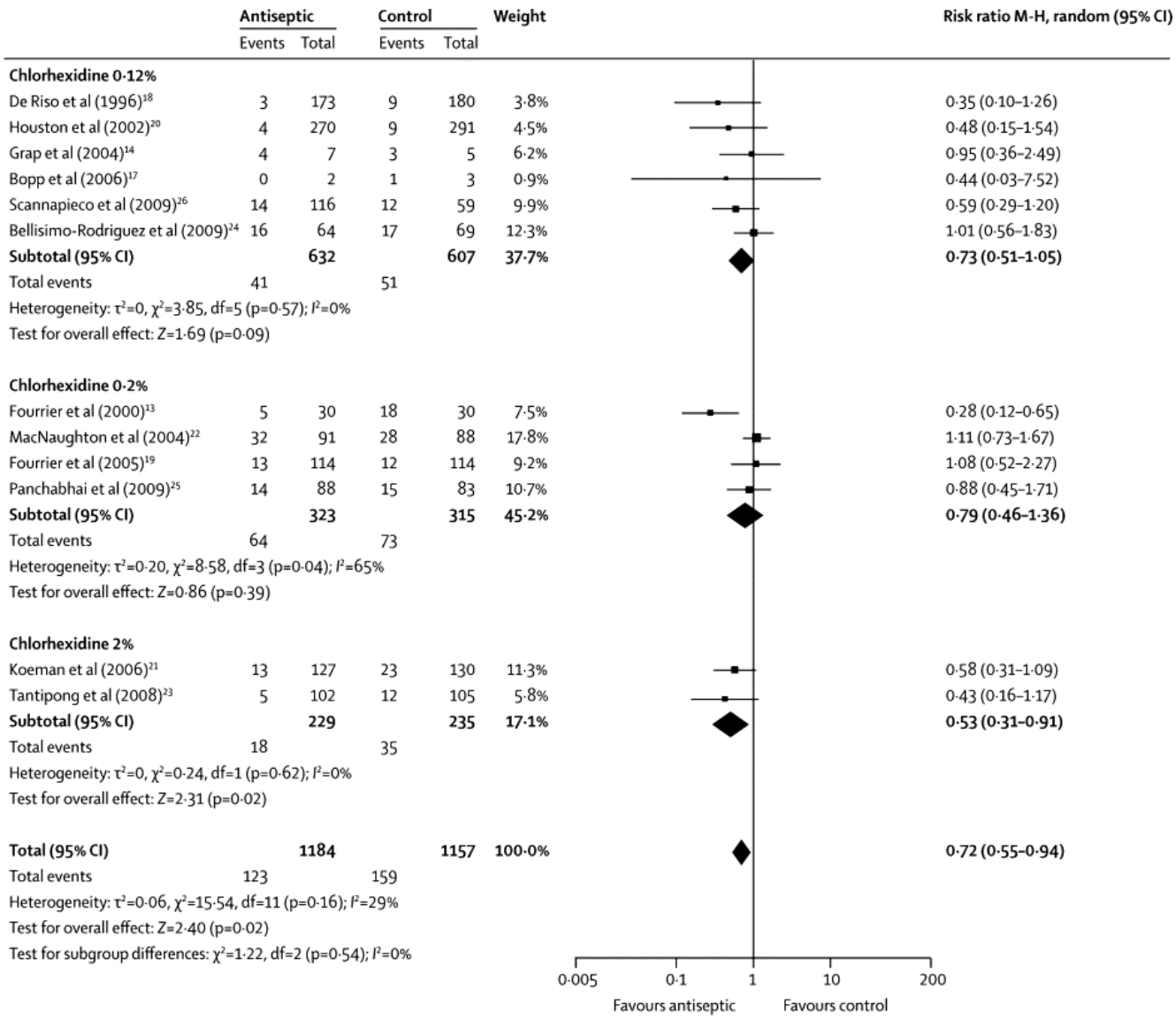

Figure 4: Subanalysis of 2%, 0.2%, and 0.12% chlorhexidine concentrations

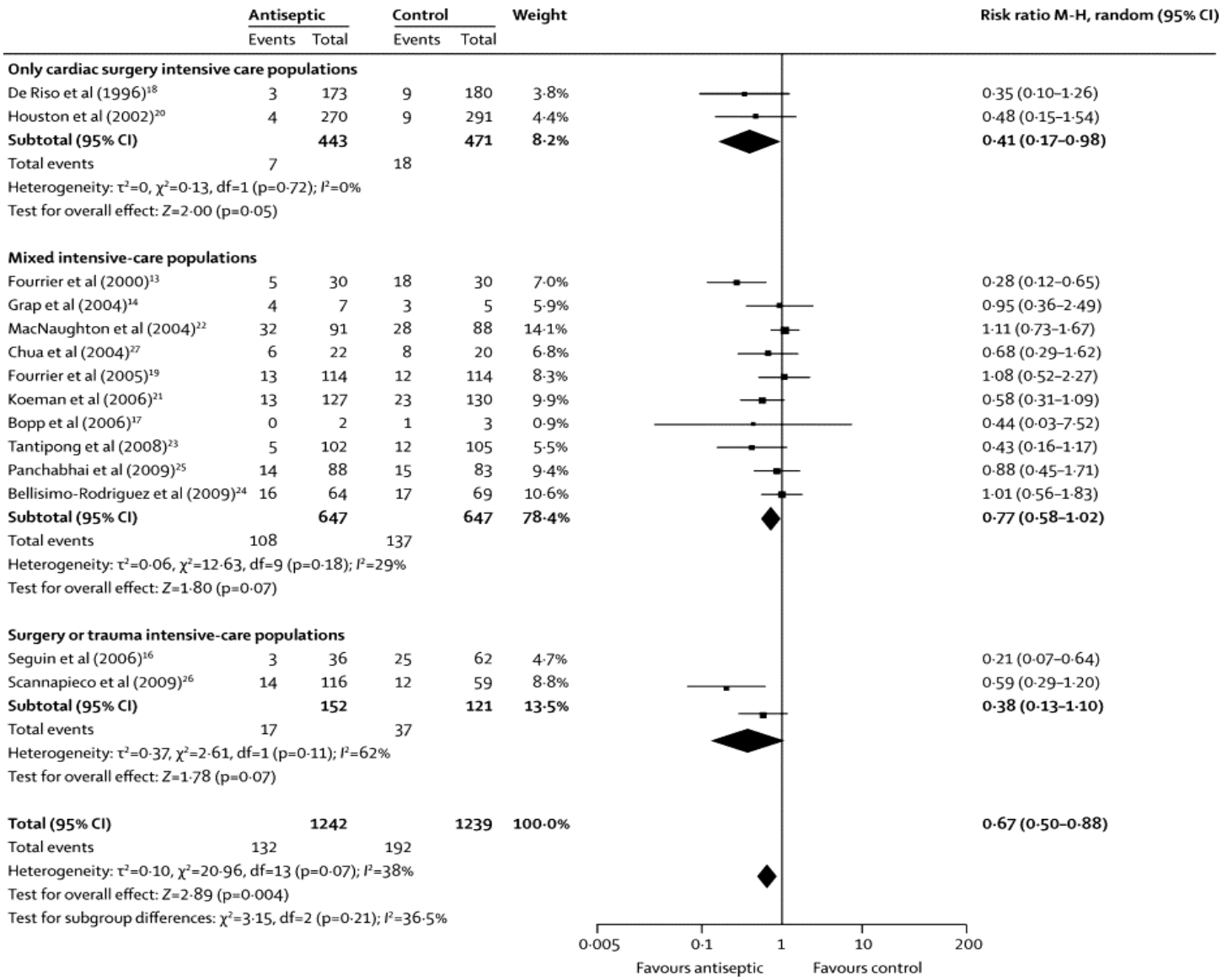

Figure 5: Subanalysis following type of intensive-care unit

to obtain more conclusive results for the use of povidone-iodine in oral care. The strengths of this analysis include the comprehensive search for relevant randomised trials, four-fold screening, assessment of methodological quality, and use of the random-effects model. This study is limited, however, by the clinical and statistical heterogeneity between the trials included. Although this lack of homogeneity was clinically perceived as substantial, statistically it was moderate in the overall meta-analysis (I^2=38%), and no evidence of heterogeneity (I^2=0%) was reported in the subanalyses of studies on cardiosurgical patients (Figure 5), and those assessing chlorhexidine at concentrations of 0.12% and 2% (Figure 4). Heterogeneity is an inherent problem in systematic reviews and meta-analyses.[279] It results from variation in sample sizes, baseline characteristics of the populations, study protocols and definitions used, diagnostic criteria, and study outcomes (positive or negative).

Furthermore, substantial clinical heterogeneity can be expected with regard to associated prevention measures. In the selected studies, information about prevention of ventilator-associated pneumonia—other than oral care—was rather scarce or absent. Besides, heterogeneity was also identified within studies, since different frequencies of care or combinations of interventions were applied.[268, 269] Although various subgroup analyses were done to elucidate the heterogeneity, insufficient data were available to analyse the effect of frequency of antiseptic application, its form, or whether teeth were brushed in combination with the intervention. Although it can be assumed that combination of different interventions for oral care might act synergetically, further research is needed to identify their specific attributable benefit on the prevention of the disease.

During our literature search, we identified other studies[198, 280-282] assessing the effect of chlorhexidine on occurrence of ventilator-associated pneumonia. These studies, however, did not meet our inclusion criteria, or the provided data were incomplete. Because we were unable to obtain the necessary data, these studies could not be included. Although effects are unlikely to be less explicit in blinded studies, our subanalysis of these trials still showed a 27% risk reduction, which proved to be very close to statistical significance.

Cardiosurgical patients benefited considerably from topical antiseptic use. In both studies including this category of patients,[206, 270] the intervention consisted of application of chlorhexidine 0.12%. Cardiosurgical patients have nevertheless a specific profile in terms of

infection control, which hampers comparison with critically ill patients in general. Most often, cardiac surgery is an elective procedure. As such, cardiosurgical patients are usually in better physical condition than are general patients in intensive-care units. Those requiring valve surgery are moreover submitted to a thorough preoperative dental and oral control, and to tooth extraction if required. Also, cardiosurgical patients are intubated in the operating theatre under optimum and controlled conditions, whereas critically ill patients are more often emergently intubated, in less optimum circumstances.

Considering all the above, it is not surprising that the beneficial effects from oral care on occurrence of ventilator-associated pneumonia in cardiosurgical patients (RR 0.41) largely exceed those in mixed intensive-care-unit patients (RR 0.77). Finally, cardiosurgical patients generally have less confounders and experience a shorter period of mechanical ventilation than do medical or trauma patients. Thereby, oral antiseptics could be assumed to be more successful in the prevention of early onset compared with late onset ventilator-associated pneumonia, occurring 5 days or more after endotracheal intubation. Due to a lack of available data, however, the present review remains inconclusive on this issue.
Our meta-analysis is the first to include studies assessing povidone-iodine. Moreover, it includes five studies that have not been included in any previous meta-analysis.

Previous meta-analyses assessing the effect of oral antiseptics on rates of ventilator-associated pneumonia[207, 208, 283, 284] had different scopes. Chan and colleagues[207] assessed, besides antiseptics, the effect of oral antibiotics on rates of ventilator-associated pneumonia. Chlebicki and Safdar,[208] Kola and Gastmeier,[284] and Pineda and colleagues[284] focused on oral care with chlorhexidine only.

In conclusion, this meta-analysis provides strong evidence of the beneficial effect of oral antiseptics in the prevention of ventilator-associated pneumonia, especially in cardiosurgical patients and with use of 2% chlorhexidine.

4. Clinicians' Adherence to Guidelines

Based on the book chapter: Labeau S, Vandijck D, Blot S. Implementation strategies for the prevention of healthcare-associated infection. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine 2010*. Berlin: Springer; 2010: 244-256.

4.1. Do healthcare workers adhere to evidence-based guidelines?

Since the beginning of their successful rise, guidelines were considered to be the perfect tool for closing the gap between what clinicians do and what scientific evidence supports. Soon, however, it became clear that, once developed, guidelines are far from being self-implementing.[21] Overall, assessments of healthcare workers' compliance with guidelines demonstrate limited adherence rates.[27, 29, 31, 33, 77, 285-288] Also in the field of infection prevention, compliance with the recommendations seems to be restricted, as illustrated by the examples listed below.[23, 34, 289, 290]

For many years, hand hygiene is commonly known to be the cornerstone of infection prevention. Although the evidence-based recommendations for performing good hand hygiene are crystal-clear, wide-spread and readily available, compliance still remains a key problem with reported compliance rates of 40%.[290]

Rello and colleagues investigated physicians' adherence to evidence-based guidelines for the prevention of VAP by means of a questionnaire and found an overall self-reported non-adherence rate of 37%.[34] Ricart et al. used the same questionnaire in a sample of ICU nurses and found the non-adherence rate to be 22.3%.[23] Moreover, as self-reports on behavior are known to be coloured by social desirability, it can be presumed that the actual non-adherence rates are even higher.

Rickard et al. conducted a survey of unit policies regarding adherence to the CDC guidelines for preventing intravascular catheter-related infections in 14 Australian ICUs.[14, 289] They found a wide diversity of practices and the absence of consistent adherence to the guidelines. Studies by Rubinson and colleagues[24, 291] also investigated adherence to the CDC guidelines for the prevention of infections associated with the use of central venous catheters, but focussing on internists in the United States. Strikingly, they identified the adherence rate with full maximal barrier precautions for catheter insertion to be 28.2% only.

Castella et al.[25] observed the application of procedures recommended for the prevention of SSI in the general surgery departments and the operating rooms of 49 hospitals in Italy. Their results highlighted a wide range of practices that could be improved with corrective interventions, among them the noticeable finding that in 60% of operations, hair removal was performed the day before the operation, and in 75% of operations by razor shaving.[25]

Noteworthy, Gammon et al.[287] conducted a review of the evidence for suboptimal compliance of healthcare practitioners to standard/universal infection control precautions, assessing reports published between 1994 to 2006. Thirty-seven studies were included in the review: 24 were related to measuring healthcare workers' compliance and 13 evaluated the impact of an intervention on adherence rates. Compliance with infection control precautions was found to be internationally suboptimal. Wide variations in the adherence to specific aspects of standard/universal precautions were reported to prevail, and healthcare workers appear to be selective in their application of recommendations.[287]

4.2. Barriers and facilitators for adherence

About clinicians' reasons for non-adherence, numerous reports and theories are available. There is a general consensus that potential barriers and facilitators are the major players involved. Information on these barriers and facilitators can be obtained in various ways, including interviews, surveys, focus groups, Delphi methods, observation, auditing records of routinely collected data, and analysis of documents.[31] Identifying and understanding the barriers and opportunities related to the adherence of evidence-based recommendations is a crucial first step in guideline implementation.[100] When designing an effective guideline implementation framework, local barriers and facilitators always need to be targeted, and the insights of different theories of behavior change integrated.[98, 100]

Behavior change theory can indeed provide a framework in which effective guideline implementation strategies can be integrated in order to help clinician adherence to evidence-based guidelines.[98] Grol has studied the different approaches to altering clinical practice, and linked them to different theories of change: (1) educational theories explain change by the desire to learn and to be professionally competent, while, in (2) epidemiologic theories, humans are considered rational beings who are expected to weigh the available evidence and come to a reasonable conclusion. According to (3) marketing theories,

behavior change is promoted by exposure to attractive marketing packages. (4) Behaviorist theories in turn suggest that change is influenced by numerous external factors which are applied before, during, or after the targeted change, while (5) social influence theories highlight the importance of the social group and peers. In (6) organizational theories, altering the system of care is suggested to enhance change. (7) Coercive theories, finally, propose to use pressure and control to achieve change, such as regulations and legislation.[292]

Cabana et al. developed a framework that goes beyond merely identifying barriers to guideline adherence, but also sets out these barriers in relation to behavior change (Figure 6).[35] Their model has been widely used in numerous quality improvement programs, and today still is a useful and inspiring outline to tackle non-adherence in the healthcare setting.

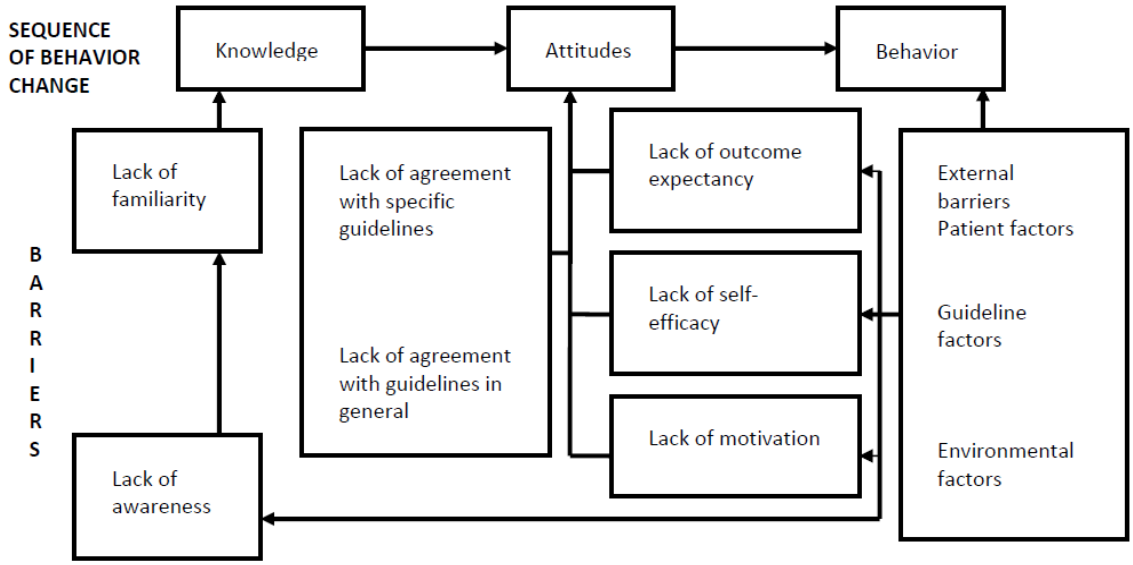

Figure 6: Model adapted from Cabana et al.[35]

4.2.1. Facilitators

Four groups of factors have been identified that enhance behavioral change and facilitate the uptake and long-term use of clinical guidelines: (1) features of the guidelines, which comprise the scientific basis for the guideline and its sources, and the way in which the guideline is presented. A clear, logical and attractive presentation should facilitate guideline acceptance and uptake. Also, guidelines that are written with high behavioral specificity and in ‘‘plain English’’ have a greater chance to be implemented than vague, hard-to-read information; (2) features of the target group, thus necessitating the implementer to

thoroughly understand the target group's level of knowledge, skills, attitudes, working practices and personalities; (3) features of the social context and the setting, which refer to the expectations and behaviors of care providers, the actual operating culture, the working routines, and the views of opinion leaders; and (4) features of the organizational context, including the financial, organizational and structural aspects of implementation, such as the availability of staff and equipment, and legal and regulatory issues.[100]

4.2.2. Barriers

Barriers impede the implementation of change. Cabana et al. conducted an extensive systematic review of the literature from January 1966 to January 1998 to identify barriers to guideline adherence.[35] Out of 76 articles, 120 surveys evaluating 293 potential barriers to physician guideline adherence were reviewed. All barriers abstracted were grouped into common themes, and then further organized into groups based on whether they affected physician knowledge, attitude, or behavior, thus setting out a framework for barrier-oriented behavior change. An adaption of this framework was outlined in Figure 6.[35]

Lack of access to hand washing sinks, insufficient time, skin irritation, ignorance about the problem, and individual preferences or habits were reported as common barriers to adherence to hand hygiene guidelines, while low staffing and high patient acuity could contribute to making compliance even more difficult.[290] Importantly, the lack of a universally accepted standard for measuring compliance was recognized as an additional major barrier.

Disagreement with the interpretation of clinical trials (35%), unavailability of resources (31.3%) and costs (16.9%) were the most common self-reported reasons for non-adherence with evidence-based recommendations for VAP prevention among a sample of physicians who were surveyed by Rello et al.,[34] while a sample of ICU nurses who were surveyed using the same questionnaire considered patient-related barriers to be significantly more important.[23]

A lack of knowledge is commonly recognized as an elemental barrier to adherence.[35, 36] Indeed, knowledge of the recommendations is doubtlessly and logically a *conditio sine qua non* for compliance. Strikingly, however, it is missing from the lists of ICU clinicians' self-reported barriers for adhering to guidelines for the prevention of nosocomial infection.[23-26, 34, 289]

Conclusion of part one

Nosocomial infection, and the *Big Four* in particular,[48] account for a considerable burden on patients and society as they are associated with increased morbidity and mortality rates, prolonged hospital and ICU stay, and with excess costs and expenditures.[57-59]

Recent trends have seen a transition from accepting healthcare-associated infection as an inevitable outcome of admission to the healthcare facility[54] towards personal accountability and a goal of zero tolerance in relation to hospital-acquired infections.[2, 3] Luckily, a considerable proportion of HAIs are preventable if the most recent evidence-based prevention recommendations are followed. [7, 67] Evidence-based infection prevention has therefore become of utmost importance in healthcare settings worldwide, and a responsibility of each and every healthcare professional.[1]

Evidence-based guidelines for the prevention of infections are widely available for healthcare workers to consult, but have been shown not to be self-implementing.[21] This is illustrated by the overall low levels of adherence to guidelines reported among healthcare workers.[27, 29, 31, 33, 77, 285-288] Sustained implementation efforts, based on a combination of multifaceted and multidisciplinary strategies with proven efficacy and efficiency, tailored to the local needs and culture, are needed to direct clinicians' daily care routines toward compliance with published recommendations.[107]

Both facilitators and barriers influence the level of success of guideline implementation strategies.[100] In the field of infection prevention, both factors have been investigated, most often by means of surveys with a self-reporting design, and comprehensively published.[23, 34, 289, 290] Among the plethora of self-reported hindrances for compliance, a lack of adequate knowledge of the guidelines' contents has, however, not been included.

The latter finding has led to the onset of the EVIDENCE-project. The first step of the project thus consisted of an assessment of the knowledge about evidence-based infection prevention guidelines among ICU nurses. The results of this needs analysis are reported in the following, second part of this thesis.

PART TWO

INTENSIVE CARE NURSES' KNOWLEDGE OF INFECTION PREVENTION GUIDELINES

"To be conscious that you are ignorant is a great step to knowledge."

Benjamin Disraeli (1804 - 1881)

Sybil, 1845

Introduction

As mentioned above, a lack of knowledge of guideline contents has never been mentioned among ICU clinicians' self-reported barriers for compliance with evidence-based recommendations for the prevention of healthcare-associated infection.[23-26, 34, 289] In 2006, we conducted a literature search aiming to detect reliable and validated instruments that could be used for evaluating healthcare workers' knowledge on this topic. No such instruments, however, were identified, thereby revealing a gap in the field of research dedicated to this particular area.

Convinced of the importance of adequate knowledge levels as a first and primordial condition for any further initiative for quality improvement, we aimed to help filling this gap by dedicating a special interest to the assessment of ICU nurses' knowledge about evidence-based guidelines for the prevention of healthcare-associated infections. As no tools were readily available, we started our project by developing multiple choice knowledge tests concerning the prevention of the *Big Four*. These questionnaires were taken through the process of validation and reliability testing.[293-295] Subsequently, they were used to assess knowledge levels of ICU nurses, with two among them on a European scale.[295-297]

Part two of this thesis relates on the process of developing multiple choice knowledge tests concerning the prevention of VAP, CVC-RI and SSI, and of the methods used for their validation and reliability testing. It moreover reports how on the local and European surveys conducted using these questionnaires.

Chapter one is dedicated to the development of and survey results obtained with the questionnaire regarding the prevention of VAP. The second chapter concentrates on the development and survey results related to the questionnaire concerning the prevention of CVC-RI. The third and last chapter reports on the development of the questionnaire concerning the prevention of SSI, and, again, on the results of the related survey.

1. Knowledge about evidence-based guidelines for the prevention of ventilator-associated pneumonia

1.1. Development of an evaluation questionnaire

Based on the article: Labeau S, Vandijck D, Claes B, Van Aken P, Blot S. Critical care nurses' knowledge of evidence-based guidelines for preventing ventilator-associated pneumonia: An evaluation questionnaire. Am J Crit Care. 2007;16(4):371-377.

Introduction

Ventilator-associated pneumonia (VAP) is defined as a pneumonia developing more than 48 to 72 hours after initiation of mechanical ventilation.[10, 49-51] With an incidence of 8% to 68%,[298, 299] VAP is the most common hospital-acquired infection among patients who require ventilatory support.[72, 299, 300] Moreover, VAP is associated with high morbidity and mortality rates, increased duration of ventilatory support and hospitalization, and increased use of healthcare resources.[58, 158, 301-303]

Prevention of VAP focuses on reduction of exposure to mechanical ventilation by preferring non-mechanical ventilation when possible and minimizing duration when mechanical ventilation is necessary,[304, 305] on avoiding microaspiration of subglottic secretions, preventing oropharyngeal colonization with exogenous pathogens, and preventing contamination of ventilator equipment.[12, 264, 298] Evidence-based guidelines for the prevention of VAP have been developed[10, 12, 306] and have been promoted by programs and campaigns of authoritative organisations.[307, 308] Nevertheless, non-adherence to these guidelines has been reported.[23, 34, 298, 309] Also, the results of assessments of nurses' knowledge of evidence-based practice in general[310-312] have been disappointing. Recently, lack of knowledge was indicated as a barrier for non-adherence to evidence-based practice.[311] Although knowledge does not ensure adherence, misconceptions about effective prevention strategies can be important in decision-making. The reduction in the rates of hospital-acquired infection[69, 313] that occurred after educational programs on strategies to prevent infection provide indirect evidence for the value of knowledge.

Our objective was to develop a reliable and valid questionnaire to determine critical care nurses' knowledge of evidence-based guidelines for preventing VAP.

Methods

Selection of Interventions and Design of the Questionnaire

The selection of interventions or strategies to prevent VAP was based on a recently published review[12] of evidence-based guidelines. In a search for relevant randomized, controlled trials and systematic reviews that involved adults that were treated with mechanical ventilation and that were published before April 2003, Dodek et al.[12] looked for physical, body positioning and pharmacologic interventions that might influence the development of VAP. Independently and in duplicate, these authors scored the validity of trials; the effect size and confidence intervals; the homogeneity of results and safety; feasibility, and economic issues. On the basis of this review[12], a total of 10 interventions or strategies with relevance for nursing practice were selected: (1) use of oral endotracheal tubes, (2) frequency of ventilator circuit changes, (3) use of a heat and moisture exchanger, (4) frequency of humidifier changes, (5) use of a closed suction system, (6) frequency of change in suction system, (7) drainage of subglottic secretions, (8) use of kinetic beds, (9) use of semi-recumbent positioning, (10) chest physiotherapy.

A multiple choice question with four response alternatives or options (the correct answer/response and 3 distractors or alternatives that are not the answer) was developed for each item on the list[314] (Table 4). For each test item, the response alternatives included the phrase 'I do not know' to avoid gambling by the respondents and 2 interventions with investigated preventive value. In their evidence-based clinical practice guideline for the prevention of VAP, Dodek et al.[12] advise consideration of 2 interventions, drainage of subglottic secretions and use of kinetic beds, but make no recommendation for use of these 2 because of cost concerns. Therefore, questions on these 2 interventions were designed to assess knowledge about the impact on the interventions on the risk for VAP. For two other interventions, closed suction system and frequency of ventilator circuit changes, the recommendations of Dodek et al.[12] are based on economic considerations.

Expert validation

The selected preventive interventions and questionnaire were presented to a panel of eight experts for face and content validation.[315] Experts had at least three years of experience in

an intensive care unit (ICU), a master's degree in nursing sciences (or medicosocial sciences), and a particular interest in ICU-acquired infections.

To achieve face validity, the experts were asked if all questions were clearly worded and would not be misinterpreted. For content validity, the experts evaluated the nursing relevance of the ten selected strategies by using a scale of 1 to 3, where 1 = not relevant, 2 = relevant but not necessary, and 3 = absolutely necessary. Additionally, the experts were asked if questions about any other preventive interventions should be added to the questionnaire.

The remarks of the panel were collected and discussed and were used to revise the questionnaire. After the revision, the experts examined the questionnaire again; they unanimously declared agreement with its content and clarity.

Assessment of the Questionnaire

Revising tests on the basis of test scores is an essential part of improving instruction.[314] Therefore, the items on the questionnaire were analysed to determine their level of difficulty and discrimination, and the quality of the 4 response alternatives or options for each question was evaluated.[314, 316, 317]

a) Difficulty level

The difficulty level of an item or question is defined as the proportion of respondents who answer the question correctly.[314, 316, 317] Possible values range from 0.0 to 1.0. Items that are answered correctly by more than 90% of the respondents (value >0.9) are considered too easy; items answered correctly by less than 10% of the respondents (value <0.1) are considered too difficult.

b) Item discrimination

A discrimination index indicates the extent to which items on the questionnaire discriminate between high scorers and low scorers. The following formula was used to divide respondents into high scorers and low scorers, with 27% of respondents in each group:

$$\frac{\text{number of correct answers in the high-scorer group} - \text{number of correct answers in low-scorer group}}{\text{total number of correct answers in both groups}}$$

Values of 0.35 and higher are (very) good; values from 0.25 to 0.35 are satisfying/good; values 0.15 to 0.25 are mediocre/satisfying; and values less than 0.15 are bad/mediocre.

c) Quality of the Response Alternatives

The quality of a response alternative is defined by calculating the proportion of respondents who choose the alternative. Values range from 0.0 to 1.0. Response alternatives with a value of 0.0 are not attractive, and those with a value of 1.0 might be too attractive.

Population Surveyed

The questionnaire was distributed and collected during the annual congress of the Flemish Society of Critical Care Nurses (Ghent, November 25, 2005). Of the 855 registered participants, 638 completed the questionnaire (response rate: 74.6%). The responses were collected anonymously. The questionnaire also included questions on general characteristics of the respondents: sex, years of ICU experience, number of ICU beds in the hospital where the respondent worked, and whether the respondent had a special degree in emergency and intensive care.

Results

Expert Validation

The experts reported that some items needed to be slightly rephrased to be clear. According to the experts, question 10 (chest physiotherapy) was irrelevant for nurses. Therefore, this question was omitted; the final questionnaire consisted of 9 items on interventions to prevent VAP.

Item Analysis

Overall values for item difficulty and discrimination were very good to satisfying (Table 4). For question 9 (patient positioning), however, the values were borderline, indicating that respondents had a good knowledge of this intervention. Nevertheless, question 9 was kept in the questionnaire because of the enormous impact of patient positioning on the prevention of VAP and the major relevance of this question for ICU nurses. Also, because the questionnaire is a criterion-referenced test, an item that is valuable for the content does not necessarily have to be excluded because the item is too easy.[318]

Table 4: Questionnaire and item analysis' results

		DIF	Q	ID
1. Oral vs. nasal route for endotracheal intubation		0.2		0.60
A*	Oral intubation is recommended		0.2	
B	Nasal intubation is recommended		0.1	
C	Both routes of intubation can be recommended		0.6	
D	I do not know		0.1	
2. Frequency of ventilator circuits changes		0.5		0.35
A	It is recommended to change circuits every 48 hrs (or when clinically indicated)		0.2	
B	It is recommended to change circuits every week (or when clinically indicated)		0.3	
C*	It is recommended to change circuits for every new patient (or when clinically indicated)		0.5	
D	I do not know		0.0	
3. Type of airway humidifier		0.5		0.30
A	Heated humidifiers are recommended		0.2	
B*	Heat and moisture exchangers are recommended		0.5	
C	Both types of humidifiers can be recommended		0.1	
D	I do not know		0.2	
4. Frequency of humidifier changes		0.1		0.55
A	It is recommended to change humidifiers every 48 hrs (or when clinically indicated)		0.6	
B	It is recommended to change humidifiers every 72 hrs (or when clinically indicated)		0.1	
C*	It is recommended to change humidifiers every week (or when clinically indicated)		0.1	
D	I do not know		0.2	
5. Open vs. closed suction systems		0.2		0.40
A	Open suction systems are recommended		0.0	
B*	Closed suction systems are recommended		0.2	
C	Both systems can be recommended		0.7	
D	I do not know		0.1	
6. Frequency of change in suction systems		0.2		0.65
A	Daily changes are recommended (or when clinically indicated)		0.5	
B	Weekly changes are recommended (or when clinically indicated)		0.2	
C*	It is recommended to change systems for every new patient (or when clinically indicated)		0.2	
D	I do not know		0.1	
7. Endotracheal tubes with extra lumen for drainage of subglottic secretions		0.6		0.30
A*	These endotracheal tubes reduce the risk for VAP		0.6	
B	These endotracheal tubes increase the risk for VAP		0.0	
C	These endotracheal tubes do not influence the risk for VAP		0.1	
D	I do not know		0.3	
8. Kinetic vs. standard beds		0.5		0.50
A	Kinetic beds increase the risk for VAP		0.0	
B*	Kinetic beds reduce the risk for VAP		0.5	
C	The use of kinetic beds does not influence the risk for VAP		0.2	
D	I do not know		0.3	
9. Patient positioning		0.9		0.10
A	Supine positioning is recommended		0.0	
B*	Semi-recumbent positioning is recommended		0.9	
C	The position of the patient does not influence the risk for VAP		0.1	
D	I do not know		0.0	
10. Chest physiotherapy**				
A	Chest physiotherapy reduces the risk for VAP			
B	Chest physiotherapy does not reduce the risk for VAP			
C	The influence of chest physiotherapy on the risk for VAP is unknown			
D	I do not know			

* correct answer

** question omitted after experts' validation

DIF: Item difficulty

Q: Quality of the option

ID: Item discrimination

In the analysis of the quality of the response alternatives, some had values of 0.0, suggesting that reformulation should be considered. Nevertheless, this finding may also indicate that inclusion of the standard response alternative “I do not know” restrained respondents from gambling. Additionally, because the response alternatives were restricted to interventions with an investigated preventive value, our formulation possibilities were limited. Of note, the score for the question 9 (patient positioning) option “Supine positioning is recommended” was 0.0, although this intervention is often used in daily practice. Therefore, despite its low score, this option was not changed for the final version of the questionnaire.

The quality of the response alternatives also indicated the extent of existing misconceptions about the preventive value of certain interventions. The responses to the final questionnaire indicated that nurses thought that both the oral and nasal routes for intubation were recommended (value 0.6); however, the oral route (value 0.2) is recommended in the guidelines. Respondents also thought that a change of humidifiers every 48 hours (or when clinically indicated) was recommended (value 0.6), whereas guidelines recommend weekly changes (or when clinically indicated) (value 0.1). The respondents thought that both open and closed suction systems were recommended (value 0.7), but only closed suction systems (value 0.2) are recommended in the guidelines. For frequency of change of suction systems, nurses thought that daily changes (or when clinically indicated) were recommended (value 0.5), whereas the guidelines recommend changes for every new patient who needs mechanical ventilation (or when clinically indicated) (value 0.2).

For all four of these items, respondents are convinced that an intervention without evidence-based preventive value is preferred over the evidence-based intervention. Mapping out this kind of widely spread misconceptions is important for better focussing education of critical care nurses.

Characteristics of the Sample

Most of the 638 respondents were women (n = 472, 74%; Table 5). A total of 274 respondents (43%) had more than 10 years of ICU experience, and 274 worked in units with more than 15 beds. Most respondents (n = 437, 68%) had a special degree in intensive care and emergency nursing.

Table 5: General characteristics of the population surveyed (n=638)

n = 638

ICU experience	**< 1 year**	**1-5 years**	**6-10 years**	**> 10 years**
	n = 153 (24%)	n = 111 (17.0%)	n = 100 (16%)	n = 274 (43%)
ICU beds	**< 8 beds**	**8 – 15 beds**	**15 beds**	**missing**
	n = 104 (16%)	n = 177 (28%)	n = 274 (43%)	n = 83
Degree	**holding degree**		**no degree**	
	n = 201 (32%)		n = 437 (68%)	
Gender	**male**		**female**	
	n = 166 (26%)		n = 472 (74%)	

Discussion and limitations

We developed a reliable questionnaire for evaluating critical care nurses' knowledge on evidence-based guidelines for preventing VAP. Face and content validity were achieved. As a result of experts' validation, the original 10-item questionnaire was adapted and reduced to nine items.

In the United States, some of the interventions mentioned in the questionnaire, such as frequency of ventilator circuit changes and frequency of humidifier changes, are implemented by respiratory care practioners. In Belgium, where this study was conducted, and in the rest of Europe, these 2 interventions are implemented by critical care nurses. We are convinced that all the interventions mentioned in the questionnaire are relevant for critical care nurses because nurses have a major role in monitoring patients' care to determine if best practices are followed. Additional interventions or strategies that are directly under the control of nurses in both the United States as in Europe, such as chlorhexidine mouth rinse, were not included in our questionnaire because the questions address only evidence-based interventions from the review by Dodek et al.[12]

Item analysis of the questionnaire was based on the responses of 638 nurses who attended the annual congress of the Flemish Society of Critical Care Nurses. This convenience sampling may have led to selection bias and may have created a barrier to extrapolating our results. Nevertheless, our sample represents 21% of all Flemish critical care nurses. Moreover, this bias should be limited because the federal government in Belgium requires

all critical care nurses who have a special degree in intensive care and emergency nursing to attend at least 16 hours a year of continuing education to maintain the degree.
Finally, guidelines can change over time. Adaptation and re-evaluation of the questionnaire will be needed each time new evidence-based interventions for preventing VAP are discovered.

Conclusion

A reliable questionnaire was developed to assess critical care nurses' knowledge on evidence-based interventions for preventing VAP. Face and content validity were achieved. The results of surveys with this questionnaire can be used to focus educational programs on VAP. The questionnaire also can be used before and after educational programs to assess the effect of the programs on nurses' knowledge of interventions to prevent VAP.

1.2. Flemish ICU nurses' knowledge of evidence-based VAP prevention

Based on the article: Labeau S, Blot SI, Vandijck DM, Van Aken P, Claes B. Evidence-based guidelines for the prevention of ventilator-associated pneumonia. Results of a knowledge test among intensive care nurses. Intensive Care Med. 2007;33(8):1463-1467.

Introduction

Ventilator-associated pneumonia (VAP) leads to a considerable excess in morbidity and mortality, and to a significant economic burden.[58, 158] Prevention of VAP primarily focusses on avoiding microaspiration of subglottic secretions, preventing oropharyngeal colonization with exogenous pathogens and contamination of ventilator equipment. Although research efforts have been undertaken to determine the value of numerous preventive measures, interpretation of the results is not always obvious.[319] There may be flaws in the study design and results from different studies may not be concordant. The positive effect of preventive measures may decrease with length of time at risk. So has continuous aspiration of subglottic secretions a favourable effect on the incidence of early onset VAP, but the effects on late onset VAP are less convincing.[192, 320-322] Also, preventive measures may be effective but too expensive for general implementation.[12, 323, 324] In response to the complexity of the issue, studies of expert panels have resulted in evidence-based guidelines.[12, 325]

Surveys evaluating compliance of practices with the recommendations have been published.[23, 34, 298, 309] Yet, to our knowledge, surveys evaluating knowledge of guidelines for VAP prevention by means of a knowledge test have not been performed. While knowledge does not insure adherence, a lack of knowledge may be a barrier to adherence. This study aimed to determine intensive care nurses' knowledge of evidence-based recommendations[12] for VAP prevention.

Materials and methods

A multiple-choice questionnaire (Table 6) was developed,[293] following the evidence-based VAP prevention guidelines by Dodek et al.[12] Selection of its items was limited to strategies with a major importance for nursing practice and adapted to an expert validation panel's comments.[293]

Demographic data gathered were gender, years of experience in an intensive care unit (ICU), number of critical beds in the hospital where respondents are put to work, and whether they hold a degree in emergency and intensive care. This degree can be achieved after the basic three year nursing education (Bachelor degree) and is acknowledged as a Bachelor-after-Bachelor degree. Although it is not obligatory to hold this degree to work in a Flemish ICU, it is strongly promoted by hospital directors since ICU licenses depend on a minimum number of nurses employed, holding this special degree (50%).

The questionnaire was distributed during the annual congress of the Flemish Society for Critical Care Nurses (Ghent, November 25, 2005) and presented plenary by a Board member. The contextual framework was explained and some time was provided to fill in the demographic data. Then, each question was read aloud while projected in the congress hall. Thirty seconds were left between two questions. Finally, the questionnaires were collected immediately after this procedure.

Continuous variables are described as median (interquartile range). Chi-square test, Mann-Whitney U test and Kruskal-Wallis test were used as appropriate. Relationships between total scores and demographic data were assessed using linear regression analysis. Variables with $p>0.15$ were stepwise removed from the regression model. Statistical analysis was performed using SPSS for Windows 12.0.0 (SPSS, Chicago, IL, US).

Table 6: Nurses' answers on the nine items of the questionnaire

Item		% of answers
1. Oral vs. nasal route for endotracheal intubation		
	Oral intubation is recommended	18.7*
	Nasal intubation is recommended	11.1
	Both routes of intubation can be recommended	59.6
	I do not know	10.7
2. Frequency of ventilator circuits changes		
	It is recommended to change circuits every 48 hrs (or when clinically indicated)	19.4
	It is recommended to change circuits every week (or when clinically indicated)	27.4
	It is recommended to change circuits for every new patient (or when clinically indicated)	48.6*
	I do not know	4.5
3. Type of airway humidifier		
	Heated humidifiers are recommended	17.2
	Heat and moisture exchangers are recommended	54.7*
	Both types of humidifiers can be recommended	12.5
	I do not know	15.5
4. Frequency of humidifier changes		
	It is recommended to change humidifiers every 48 hrs (or when clinically indicated)	58.8
	It is recommended to change humidifiers every 72 hrs (or when clinically indicated)	11.4
	It is recommended to change humidifiers every week (or when clinically indicated)	13.3*
	I do not know	16.5
5. Open vs. closed suction systems		
	Open suction systems are recommended	3.3
	Closed suction systems are recommended	16.9*
	Both systems can be recommended	69.3
	I do not know	10.5
6. Frequency of change in suction systems		
	Daily changes are recommended (or when clinically indicated)	45.1
	Weekly changes are recommended (or when clinically indicated)	22.3
	It is recommended to change systems for every new patient (or when clinically indicated)	19.6*
	I do not know	13.0
7. Endotracheal tubes with extra lumen for drainage of subglottic secretions		
	These endotracheal tubes reduce the risk for VAP	60.3*
	These endotracheal tubes increase the risk for VAP	3.6
	These endotracheal tubes do not influence the risk for VAP	8.2
	I do not know	27.9
8. Kinetic vs. standard beds		
	Kinetic beds increase the risk for VAP	1.3
	Kinetic beds reduce the risk for VAP	48.7*
	The use of kinetic beds does not influence the risk for VAP	19.3
	I do not know	30.7
9. Patient positioning		
	Supine positioning is recommended	0.8
	Semi-recumbent positioning is recommended	90.3*
	The position of the patient does not influence the risk for VAP	5.5
	I do not know	3.4

*Correct answer; VAP: ventilator-associated pneumonia

Results

Of the 855 registered participants of the congress, 638 completed the questionnaire (74.6%). Most respondents were female (n=472; 74.0%). About 1/4 (n=153; 24.0%) had <1 year of ICU experience, 111 (17.4%) 1 to 5 years, 100 (15.7%) 6 to 10 years, and 274 (43.0%) >10 years. A majority (n=274; 42.9%) worked in a hospital with >15 ICU beds, 177 (27.7%) with 8 to 15

beds and 104 (16.3%) with <8 beds. A degree in emergency and critical care was held by 68% (n=437). Nurses from 91 ICUs attended the congress.

The questionnaire and nurses' answers are shown in Table 6. Average scores according to respondents' characteristics are demonstrated in Table 7. The average score was 3.7 on 9 questions (41.2%). No substantial differences were found between males and females, nor did the number of beds affect the results. Nurses with <1 year experience performed worse than nurses with >1 year experience. Nurses holding the degree had significantly better scores than those not holding it. Linear regression analysis identified years of experience (per class increase) and degree as independently associated with better knowledge (Table 8).

Table 7: Average scores on nine questions according to respondents' characteristics

Characteristic	Mean (%)	Median (interquartile range)	p
Total cohort	3.71 (41.2)	4 (3 – 5)	-
Gender			0.545
Female	3.69 (41.0)	4 (3 – 5)	
Male	3.77 (41.9)	4 (3 – 5)	
Number of ICU beds			0.401
<8 beds	3.72 (41.3)	4 (2 – 5)	
8 – 15 beds	3.97 (44.1)	4 (3 – 5)	
>15 beds	3.93 (43.7)	4 (3 – 5)	
Years of ICU experience			<0.001
<1 year	2.85 (31.7)	3 (2 – 4)	
1 – 5 year	3.70 (41.1)	4 (3 – 5)	
6 – 10 years	4.16 (46.2)	4 (3 – 5)	
>10 years	4.03 (44.8)	4 (3 – 5)	
Special title in emergency and intensive care			<0.001
Yes	3.94 (43.7)	4 (3 – 5)	
No	3.22 (35.8)	3 (2 – 4)	

Table 8: Adjusted relationships with the average knowledge

	B ± standard error	95% confidence interval	p
ICU experience (per class increase)*	0.31 points** ± 0.05	0.20 – 0.41	<0.001
Degree in emergency and critical care	0.32 points** ± 0.14	0.03 – 0.58	0.032

*classes are <1 year, 1-5 years, 6-10 years, or >10years of ICU experience;
**on a total of nine (one point per question);
R^2=0.1

Discussion

We evaluated Flemish nurses' knowledge of VAP guidelines. Overall the results were poor. Our results can be compared with four previously published reports.[23, 34, 298, 309] Rello et al. distributed a questionnaire in 22 countries to indicate whether practices were according to a recent review article, thus identifying barriers to physicians' adherence to guidelines.[34] The

study by Heyland et al. described the use of strategies for VAP prevention prior to publication of the Canadian Critical Care Trials Group's guidelines.[298] In the survey by Sierra et al., practices on prevention and diagnosis of VAP were explored among physicians in 28 Spanish ICUs.[309] The study by Ricart et al. focusses on nursing adherence to VAP guidelines.[23] The utmost important difference between our study and those reporting care practices[23, 34, 298, 309] is that our questionnaire was designed to measure knowledge. Nevertheless, we assume that our results also reflect, at least to some extent, practice in Flemish ICUs.

Sierra et al. found that in 75% of the ICUs ventilator circuits were changed every 72 hours or later.[309] This is in accordance with our findings where nurses indicated to change circuits weekly or later in 76%. Fifty-five% of our respondents identified heat and moisture exchangers as the recommended type of airway humidification. In the studies by Heyland et al., Ricart et al., and Sierra et al., respectively 80%, 84%, and 96% of the respondents used heat and moisture exchangers.[23, 298, 309]

It is recommended to change airway humidification systems weekly or when clinically indicated.[12] Only 12% of our respondents were aware of this recommendation, suggesting that, in daily practice, humidification systems are changed too frequently. Also in the studies by Rello et al. and Ricart et al., heat and moisture exchangers were changed on a daily basis in 59% and 75% respectively.[23]

In our survey only 17% recognized closed systems as recommended. In Canada closed suction systems are used in 88% of the ICUs, while in Spain open tracheal suctioning was reported in 96% of the ICUs.[23, 34, 298, 309] In Flanders, closed suction systems are not commonly used, results of our survey thus reflecting nurses' unfamiliarity with those systems.

Sixty% knew that draining subglottic secretions decreases the risk for pneumonia. The beneficial effect of kinetic beds was recognized by about half of the nurses. However, for these two issues, respectively 28% and 31% of nurses reported not to know the answer, this suggesting that these strategies are seldom used in Flemish ICUs. Finally, in our survey semi-recumbent positioning was well acknowledged to prevent VAP.

Generally, more experienced nurses had a higher knowledge level than those with <1 year experience. The knowledge level among nurses holding a special degree was also higher

(Table 7). After adjustment for years of ICU experience, the advantage of the special degree remained significant (Table 8).

Our findings demonstrate that nurses' awareness about VAP guidelines is low, and stress the need for thorough education based on current recommendations. One might question the importance of pure knowledge versus degree of application in practice. We believe that thorough understanding of the recommended strategies supports adherence and overcomes potential barriers as previously identified.[23, 34] Additionally, increasing the average level of knowledge has been the first step in successful multifaceted educational programs.[69, 264, 326] Guidelines themselves only have a limited impact on changing behaviour. Within institutions, efforts must be taken to organize educational programs to fine-tune practice with guidelines. The favourable value of such programs has been demonstrated.[327-329]

As all surveys, the present study suffers from selection bias. Individuals with a higher interest in the topic are more likely to participate. Moreover, the questionnaire was distributed at the annual congress of the Flemish Society for Critical Care Nurses. Nurses attending congresses might be more skilled or motivated. However, this bias is limited by the fact that the federal government requests at least 16 hours of education yearly, to maintain the degree.

Additionally does knowledge of recommendations not necessarily reflect practice. Nurses may change ventilator circuits for every new patient, not knowing this is a guideline. Moreover, no weights were linked to the different strategies' relative importance. For example, supine positioning can be considered as a higher risk for VAP than changes of heat and moisture exchangers per 48 hours. In this way, the higher scores achieved for patient positioning and subglottic secretions drainage are in favour of the study population.

This study is a preliminary investigation in a strict geographical region. Its results cannot be extrapolated. A multi-country study should be conducted to draw more general conclusions. Despite the geographical restriction, our major strength is the large sample size. We collected 638 questionnaires. The number of Flemish ICU nurses being approximately 3000, our sample covers >20% of potential respondents.

In conclusion, Flemish nurses' knowledge of VAP prevention guidelines is low. Their education should include supplementary support from current evidence-based guidelines.

1.3. European ICU nurses' knowledge of evidence-based VAP prevention

Based on the article: Labeau S, Vandijck D, Rello J, Adam S, Rosa A, Wenisch C, Bäckman C, Agbaht K, Csomos A, Seha M, Dimopoulos G, Vandewoude K, Blot S, for the EVIDENCE-study investigators. Evidence-based guidelines for the prevention of ventilator-associated pneumonia: results of a knowledge test among European intensive care nurses. J Hosp Infect. 2008;70(2):180-185.

Introduction

Nosocomial infections concern 5% to 35% of patients admitted to the intensive care unit (ICU) and 50% to 60% of patients remaining in the ICU for more than five days.[49, 301] This is associated with prolonged hospital stay, increased morbidity and mortality, and important additional costs for patient and society.[54] Infection prevention is considered a priority in the ICU and an important indicator of quality of care.

Structured multifaceted interventional programmes have a positive influence on nosocomial infection rates.[69] The first step in such programmes is to provide education, in order to increase awareness of evidence-based infection control practice.[69] Adult learning theory, focusing on learner involvement in the learning process, has substantially changed medical education over the past three decades, but its influence is not yet widespread in web-based teaching.[330]

With the EVIDENCE-project, we aim to develop a website-based e-learning platform for ICU nurses on infection prevention (URL: www.vvizv.be/Pages/Evidence.php). As the first step in any educational endeavour is needs analysis,[330] we started our study by assessing our target group's knowledge of measures for infection prevention. We report the results here of a knowledge test on evidence-based VAP prevention guidelines among 3329 European ICU nurses.

Methods

For assessing nurses' knowledge of measures for infection prevention, reliable and validated multiple-choice questionnaires were developed (Table 9).[293, 294] The evidence-based guidelines by Dodek et al. were used as standard for developing a questionnaire on VAP prevention recommendations.[12, 293]

Table 9: Nurses' answers on multiple choice questions

Item		% of answers
1. Oral vs. nasal route for endotracheal intubation		
	Oral intubation is recommended	54.7*
	Nasal intubation is recommended	5.8
	Both routes of intubation can be recommended	33.0
	I do not know	6.5
2. Frequency of ventilator circuits changes		
	It is recommended to change circuits every 48 hrs (or when clinically indicated)	19.4
	It is recommended to change circuits every week (or when clinically indicated)	42.2
	It is recommended to change circuits for every new patient (or when clinically indicated)	35.1*
	I do not know	3.3
3. Type of airway humidifier		
	Heated humidifiers are recommended	22.0
	Heat and moisture exchangers are recommended	38.2*
	Both types of humidifiers can be recommended	24.6
	I do not know	15.2
4. Frequency of humidifier changes		
	It is recommended to change humidifiers every 48 hrs (or when clinically indicated)	49.6
	It is recommended to change humidifiers every 72 hrs (or when clinically indicated)	12.5
	It is recommended to change humidifiers every week (or when clinically indicated)	21.4*
	I do not know	16.7
5. Open vs. closed suction systems		
	Open suction systems are recommended	9.1
	Closed suction systems are recommended	45.7*
	Both systems can be recommended	39.5
	I do not know	5.6
6. Frequency of change in suction systems		
	Daily changes are recommended (or when clinically indicated)	61.7
	Weekly changes are recommended (or when clinically indicated)	13.5
	It is recommended to change systems for every new patient (or when clinically indicated)	18.2*
	I do not know	6.6
7. Endotracheal tubes with extra lumen for drainage of subglottic secretions		
	These endotracheal tubes reduce the risk for VAP	50.6*
	These endotracheal tubes increase the risk for VAP	5.9
	These endotracheal tubes do not influence the risk for VAP	10.1
	I do not know	33.4
8. Kinetic vs. standard beds		
	Kinetic beds increase the risk for VAP	3.1
	Kinetic beds reduce the risk for VAP	57.3*
	The use of kinetic beds does not influence the risk for VAP	18.9
	I do not know	20.7
9. Patient positioning		
	Supine positioning is recommended	3.2
	Semi-recumbent positioning is recommended	85.1*
	The position of the patient does not influence the risk for VAP	6.5
	I do not know	5.2

To establish a European network, 31 potential were identified by searching the electronic database *Pubmed* for researchers with a particular interest in ICU infections. They were invited to act as a national representative beginning of October 2006. Representatives were engaged to distribute the questionnaire nationally among ICU nurses and to the completed copies via postal mail by 1 March 2007. Of 31 potential collaborators contacted, 26 agreed to cooperate and were mailed the questionnaire in mid-October 2006. They informed and

instructed local ICU nurses through responsible hospital staff. Monthly newsletters helped strengthen the network.

Demographics included nationality, gender, ICU experience, number of ICU beds, and acquisition of a postgraduate degree in intensive care, provided by a higher education institution or similarly professionally accredited organisation. The questionnaire comprised 9 questions; one point was given for each correct answer; a wrong answer did not affect the score negatively. A maximal score thus consisted of nine and a minimal score of zero points.

For statistical analysis SPSS 13.0.0 for Windows was used (SPSS, Chicago, IL, US). Continuous variables are described as median (interquartile range). Chi-square, Mann-Whitney *U*-tests and Kruskal-Wallis tests were used as appropriate. Relationships between total scores and demographics were assessed by means of a linear regression analysis. Variables with $p>0.15$ were stepwise removed from the regression model.

Results

Data were obtained from 22 out of 26 countries that had agreed to participate, corresponding with 3329 questionnaires (Table 10). As for the four remaining countries, communication was stopped by the potential collaborators and no questionnaires were returned. The global response rate was 69.1%. The questionnaire and the distribution of the nurses' answers among its answering alternatives are shown in Table 9. Table 11 shows the nurses' scores in relation to their characteristics.

The average score was 4.06 on nine questions (45.1%). More experienced nurses performed significantly better than their less-experienced colleagues ($p<0.001$ for <1 year vs. >1 year; $p<0.001$ for <5 years vs. >5 years and $p=0.001$ for <10 years vs. >10 years ICU experience, respectively). Scores of nurses from larger ICUs were significantly lower than those of respondents from smaller units ($p<0.001$ for <8 beds vs. >8 beds; and $p=0.048$ for <15 beds vs. >15 beds, respectively).

Linear regression analysis ($R^2=0.12$) showed ICU experience (per class of increase: <1 year, 1-5 years, 6-10 years, or >10 years of experience) to be independently associated with better test scores ($p<0.001$; B ± standard error 0.09 points ± 0.02; confidence interval 0.04 – 0.14). An increase in class of the number of ICU beds (<8 beds, 8-15 beds, or >15 beds) was associated with lower scores ($p<0.001$; B ± standard error -0.15 points ± 0.03; confidence

interval -0.02 – -0.09). No independent relationships between gender (p=0.51) or nationality (p=0.75) and test scores were identified.

Table 10: Questionnaires received per country

Country	# questionnaires	%
Austria	204	6.1
Belgium	686	20.6
Czech Republic	15	0.5
Denmark	31	0.9
Finland	121	3.6
Germany	138	4.1
Greece	174	5.3
Hungary	178	5.3
Italy	140	4.2
Latvia	82	2.5
Lithuania	11	0.3
Malta	43	1.3
Netherlands	93	2.8
Norway	16	0.5
Portugal	484	14.5
Slovakia	112	3.4
Slovenia	120	3.6
Spain	143	4.3
Sweden	147	4.4
Switzerland	178	5.3
Turkey	197	5.9
United Kingdom	15	0.5
Total	**3329**	100.0

Discussion

Low scores were found on a knowledge test on evidence-based VAP prevention guidelines among European ICU nurses. Interpretation of this finding requires caution, however, as the standard for the test question answers was derived from a particular set of evidence-based recommendations.[12] Marked differences are noted to exist between local and international guidelines and it is not entirely clear whether poor test scores reflect a lack of knowledge, deficiencies in training, differences in what is regarded as good practice, and/or a lack of consistent policy. If better scores are obtained after judging the participants against local guidelines, this would suggest that the problem is lack of consistent policy, rather than poor training. Indeed, there has been a rapid increase in the number of country-specific VAP guidelines, that vary in their overall recommendations, in Europe recently.[164] Development of comprehensive pan-European guidelines would help rationalise conflicting proposals, provide a useful resource and limit guideline proliferation.[164, 331]

Table 11: Average scores on nine questions according to respondents' characteristics

Characteristic	n	Mean (%)	Median (interquartile range)	*p*
Total cohort	3329	4.06 (45.1)	4 (3 – 5)	-
Gender				0.533
Female	2657	4.07 (45.2)	4 (3 – 5)	
Male	672	4.03 (44.7)	4 (3 – 5)	
Number of ICU beds				< 0.001
<8 beds	1012	4.27 (47.4)	4 (3 – 5)	
8 – 15 beds	1331	4.07 (45.2)	4 (3 – 5)	
>15 beds	887	3.98 (44.2)	4 (3 – 5)	
Years of ICU experience				< 0.001
<1 year	420	3.48 (38.6)	3 (2 – 5)	
1 – 5 year	969	4.09 (45.4)	4 (3 – 5)	
6 – 10 years	690	4.25 (47.2)	4 (3 – 5)	
>10 years	1242	4.14 (46.0)	4 (3 – 5)	
Qualification in intensive care*	2390			0.229
Yes	1257	4.08 (45.3)	4 (3 – 5)	
No	1122	4.01 (44.5)	4 (3 – 5)	

* only taking in account these participating countries where such a degree can be obtained (Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom). The total number of respondents from these countries is 2390. Percentages (numbers) may not always add up to 100 (3329) due to missing values.

Our questionnaire took no account of the costs related to recommendations. This may be an important issue in some of the emerging economies since several of the mentioned strategies (such as kinetic beds) are quite expensive. Nurses may simply not be aware of the possibilities because they are not available locally.

Non-adherence to evidence-based recommendations for VAP prevention is reported to be common.[23, 34, 174, 309, 332] Rello et al. reported an overall non-adherence rate of 37.0% among physicians.[34] Ricart et al. found the overall non-adherence rate in a sample of ICU nurses to be 22.3%.[23] In Spanish ICUs, common prevention and diagnostic procedures differed significantly from evidence-based recommendations.[309] Recently, nurses self-reported lack of consistency and uniformity in VAP guideline implementation with only half of the respondents maintaining elevation of the head of the bed if not contraindicated.[174] An Italian study, assessing ICU nurses' knowledge and application of VAP prevention guidelines, found 17.9% applying none and only 22.6% self-reporting their knowledge of VAP prevention strategies to be satisfactory.[332] Although knowledge of recommendations does not necessarily reflect practice, we recommend implementing multifaceted educational programmes on VAP prevention guidelines in European ICUs, and strongly promote nurses' participation in order to create awareness of (local) evidence-based recommendations.

Differences between scores of nurses holding and not holding a specialised degree in intensive care was minimal. Nonetheless, throughout Europe, substantial differences exist in duration, level and content of the courses leading to this degree, and in the nature and level of the institutions providing them. These differences were not considered when performing statistical analysis. In individual countries, acquisition of a specialised qualification may be associated with a better knowledge of the questionnaire's guidelines, as demonstrated in a sample of Flemish nurses.[333] For specialised ICU courses, we strongly recommend including the most recent evidence-based guidelines for infection prevention in general, and for VAP prevention in particular.

The major strength of our study is the sample size and the amount of participating countries. Our results may nevertheless suffer from selection bias. It is possible that respondents had a particular interest in infection prevention or were more motivated than nurses who did not participate in the study. If so, the scores of non-respondents might even be lower than those reported. Moreover, from some countries we collected a rather small number of questionnaires (e.g. Lithuania, United Kingdom; cf. Table 10). These results may be less representative than those from countries where a larger number of questionnaires were gathered.

In conclusion, further research might help to explain European ICU nurses' low scores on a knowledge test on VAP prevention guidelines. In the meantime, we recommend implementing multifaceted educational programmes comprising information on recent VAP prevention guidelines in the ICU, and promoting nurses' participation to maximise awareness of infection control practices.

2. Knowledge about evidence-based guidelines for the prevention of central venous catheter-related infection

2.1. Development of an evaluation questionnaire

Based on the article: Labeau S, Vereecke A, Vandijck D, Claes B, Blot S. Critical care nurses' knowledge of evidence-based guidelines for preventing infections associated with central venous catheters: an evaluation questionnaire. Am J Crit Care. 2008;17(1):65-71.

Introduction

Central venous catheters (CVC) are life-sustaining devices in the care of critically ill patients but are associated with a risk for infections that can increase morbidity and mortality and the cost of care.[14, 57, 334-336] Infections associated with intravascular catheters account for 10% to 20% of all nosocomial infections.[337] The mean rate of CVC-related bloodstream infections in the intensive care unit (ICU) is 5.3 per 1000 catheter days.[14] From 10% to 70% of all CVC-related infections are preventable.[67] Therefore, evidence-based guidelines have been published.[14, 338, 339]

The guidelines for the prevention of intravascular catheter-related infections,[14] published by the Centers for Disease Control and Prevention, provide recommendations for catheter care whose preventive value is supported by scientific research. Although the recommendations are evidence-based, non-adherence to them has been reported.[24, 69, 340] This lack of adherence may be due to a lack of knowledge of the guidelines. Research[37, 39, 41, 69, 341, 342] has indicated that education of healthcare workers, preferably as part of a multifaceted quality improvement program, can reduce the rate of CVC-related infection.

The study reported here is part of a project of our research group to determine ICU nurses' knowledge of evidence-based guidelines for preventing infections.[293, 333] Our objective was to develop a reliable and valid questionnaire that can be used to assess critical care nurses' knowledge of evidence-based guidelines for preventing CVC-related infection.

Methods

Selection of interventions and design of the questionnaire

The interventions to prevent CVC-related infection were selected on the basis of the current guidelines[14] of the US Centers for Disease Control and Prevention for the prevention of

intravascular catheter-related infections. These guidelines are supported by the results of rigorously selected clinical trials or systematic reviews and were prepared by a multidisciplinary working group of professionals in different fields of medicine and nursing.
On the basis of these guidelines, 10 interventions or strategies related to central venous catheters and with relevance for nursing practice were selected: (1) frequency of CVC changes, (2) frequency of changes in CVCs over a guidewire, (3) frequency of changes in pressure transducers and tubing, (4) use of coated CVCs, (5) frequency of changes of catheter dressing, (6) use of gauze and polyurethane catheter dressings, (7) use of 2% aqueous chlorhexidine disinfecting the insertion site, (8) use of antibiotic ointment, (9) frequency of changes in administration sets when lipid emulsions were administered, (10) frequency of changes in administration sets when neither lipid emulsions nor blood products were administered.

As in previous studies,[293, 333] a multiple-choice questionnaire with four response alternatives or options (the correct answer/response and three distractors or alternatives that are not the answer) was developed for each item on the list (Table 12). For each test item, the response alternatives included the phrase "I do not know" to avoid gambling by the respondents. The two remaining response alternatives consisted of strategies whose preventive value has not been established in evidence-based studies.

Expert validation

A panel of 7 experts examined the 10 preventive interventions and the questionnaire for face and content validation.[315] Of the experts, 6 had at least 10 years of experience in an ICU; 1, who has worked as a nursing hospital hygienist for several years, had three years of ICU experience. All 7 had at least a master's degree in nursing sciences (or medical-social sciences), and were involved, at least locally, in research on ICU-acquired infections. Methods for expert validation and questionnaire assessment were similar as reported in the paper relating on the development of the VAP questionnaire (Part Two: 1.1. Development of an evaluation questionnaire).

Population Surveyed

The questionnaire was distributed and collected during the annual congress of the Flemish Society of Critical Care Nurses (Ghent, Belgium, November 24, 2006). Of the 855 registered

participants, 762 completed the questionnaire (response rate: 89.1%). The responses were collected anonymously. The questionnaire also included questions on general characteristics of the respondents: sex, years of ICU experience, number of ICU beds in the hospital where the respondent worked, and whether the respondent had a special degree in emergency and intensive care. Such a degree can be achieved after the basic three-year nursing education (bachelor's degree) and is acknowledged as a bachelor-after-bachelor degree.

The study was approved by the ethics committee of Ghent University Hospital, Ghent, Belgium.

Results

Expert Validation

For clarity, some items needed to be slightly rephrased. The experts considered all 10 items of the questionnaire relevant for nursing practice. Table 12 shows the final questionnaire.

Characteristics of the Sample

The majority of the 762 respondents were women (n = 581, 76%). A total of 353 respondents (46%) had more than 10 years of ICU experience, and 349 (46%) worked in units with more than 15 beds. A majority of the respondents (n = 557, 73%) had a special degree in intensive care and emergency nursing (Table 13).

Item Analysis

Values ranged from 0.1 to 0.9 for item difficulty and from 0.05 to 0.41 for item discrimination (Table 12). Values were very good to satisfying for 9 of the 10 questions. For question 9 (frequency of changes in administration sets when lipid emulsions were administered), however, the values were too low, indicating that respondents had a good knowledge of this intervention. Nevertheless, question 9 was kept in the questionnaire because of the relevance of the question for ICU nurses. Also, in a criterion-referenced test such as this questionnaire, items valuable for content are not necessarily excluded because they are too easy.[318, 343]

The quality of the response alternatives was 0.0 for 9 of the 10 questions, suggesting a possible need for reformulation. However, another interpretation of this finding is that respondents refrained from gambling because of the response alternative "I do not know".

Table 12: Questionnaire

		DIF	Q	ID
1. It is recommended to replace CVCs routinely …				0.20
A	Yes, every seven days		0.2	
B	Yes, every three weeks		0.2	
C [b]	No, only when indicated	0.6		
D	I do not know		0.0	
2. It is recommended to replace CVCs over a guidewire …				0.17
A	Yes, every three days		0.0	
B	Yes, every seven days		0.1	
C [b]	No, only when indicated	0.7		
D	I do not know		0.2	
3. It is recommended to replace pressure transducers and tubing routinely …				0.38
A [b]	Yes, every four days	0.4		
B	Yes, every eight days		0.3	
C	No, only when indicated		0.3	
D	I do not know		0.1	
4. In settings with a high rate of catheter-related infections it is recommended to use a CVC coated or impregnated with an antiseptic agent …				0.34
A [b]	Yes, in patients whose CVC is expected to remain in place for more than five days	0.2		
B	No, because the use of such catheters is not cost-effective		0.1	
C	No, because the use of such catheters does not result in a significant decrease in the rate of catheter-related infections		0.4	
D	I do not know		0.4	
5. It is recommended to change the dressing on the catheter insertion site …				0.23
A	On a daily basis		0.1	
B	Every three days		0.3	
C [b]	When indicated (soiled, loosened, …) and at least weekly	0.6		
D	I do not know		0.0	
6. It is recommended to cover up the catheter insertion site with …				0.28
A	Polyurethane dressing (transparent, semipermeable)		0.7	
B	Gauze dressing		0.1	
C [b]	Both are recommended because the type of dressing does not affect the risk for catheter-related infections	0.2		
D	I do not know		0.0	
7. It is recommended to disinfect the catheter insertion site with …				0.41
A [b]	2% aqueous chlorhexidine	0.1		
B	0.5% alcoholic chlorhexidine		0.8	
C	10% povidone-iodine		0.1	
D	I do not know		0.0	
8. It is recommended to apply an antibiotic ointment at the insertion site of a CVC …				0.23
A	Yes, because it decreases the risk for catheter-related infections		0.0	
B [b]	No, because it causes antibiotic resistance	0.3		
C	No, because it does not decrease the risk for catheter-related infections		0.6	
D	I do not know		0.1	
9. When lipid emulsions are administered through a CVC it is recommended to replace the administration set …				0.05
A [b]	Within 24 hours	0.9		
B	Every 72 hours		0.1	
C	Every 96 hours		0.0	
D	I do not know		0.0	
10. When neither lipid emulsions, nor blood products are administered through a CVC it is recommended to replace the administration set …				0.30
A	Every 24 hours		0.1	
B	Every 48 hours		0.4	
C [b]	Every 96 hours	0.5		
D	I do not know		0.0	

* correct answer

DIF: Item difficulty; Q: Quality of the option; ID: Item discrimination

Table 13: General characteristics of the population surveyed (n=762)

n = 762

ICU experience	**< 1 year**	**1-5 years**	**6-10 years**	**> 10 years**
	n = 134 (18%)	n = 150 (20%)	n = 125 (16%)	n = 353 (46%)

ICU beds	**< 8 beds**	**8 – 15 beds**	**15 beds**	**missing**
	n = 109 (14%)	n = 213 (28%)	n = 349 (46%)	n = 91 (12%)

Degree	**holding degree**	**no degree**	**missing**
	n = 557 (73%)	n = 202 (26.5%)	n = 3 (0.5%)

Gender	**male**	**female**
	n = 181 (24%)	n = 581 (76%)

Additionally, possible formulations were limited because the response alternatives were restricted to interventions with an investigated preventive value.

The responses to the final questionnaire indicated that nurses had numerous misconceptions about the care of CVCs. First, that they often responded that the use of coated CVCs does not result in significant decrease of catheter-related infections (value 0.4); however the guidelines[14] recommend these catheters in settings with a high rate of catheter-related infections for patients whose CVC is expected to remain in place for more than five days. Second, the respondents chose the use of polyurethane dressings at the catheter site (value 0.7), whereas both gauze and polyurethane dressings are recommended[14] (value 0.2). Finally, the nurses selected 0.5% alcoholic chlorhexidine solution (value 0.8) over the recommended 2% aqueous chlorhexidine solution[14] (value 0.1).

All respondents thought correctly that the use of an antibiotic ointment at the catheter insertion site is not recommended. Remarkably, most nurses thought use of such an ointment is not recommended because antibiotic ointments do not decrease the risk for catheter-related infections (value 0.6), whereas the correct reason is that the use of these ointments causes antibiotic resistance (value 0.3).

For the first three items on the questionnaire (use of coated CVCs, type of catheter dressing and type of disinfection solution), respondents are convinced that an intervention without evidence-based preventive value is preferred over the evidence-based intervention. Nurses seem to have a misconception about the reason antibiotic ointments are not used at the

catheter site. Discovering this kind of widely spread misconception is important for focusing education of critical care nurses.

Discussion and Limitations

This questionnaire had both face and content validity. We did not determine construct validity, which indicates what construct a test actually measures and can be established using the known-groups technique. In this procedure, groups that are expected to differ on the critical attribute take the test, and group scores are compared.[343] In order to establish construct validity for our questionnaire, the test should be presented to a group of other than critical care nurses. The scores of the non-critical care nurses should differ from those of a group of critical care nurses. Nevertheless, CVCs are not used exclusively in the ICU; they have become frequently used devices in many units. In Flanders, CVC care is included in the curriculum of the three basic years of nursing education. Thus, knowledge of CVC-care should have become common knowledge among nurses. Establishing construct validity could support or contradict this assumption.

Use of the convenience sample of nurses attending the annual congress of the Flemish Society of Critical Care Nurses could lead to selection bias and create a barrier to extrapolating our results. Nevertheless, the 762 nurses in our sample account for 21% of all Flemish critical care nurses. Moreover, this bias can be limited because the federal government in Belgium obliges all critical care nurses who have a special degree in intensive care and emergency to attend at least 16 hours a year of continuing education in order to maintain this degree.

Finally, guidelines are revised according to the latest research and adaptation, and re-evaluation of the questionnaire will be necessary for the prevention of CVC-related infection.

Conclusion

The questionnaire developed to assess critical care nurses' knowledge of evidence-based strategies for the prevention of CVC-related infection is reliable and has face and content validity. The questionnaire can be used before and after an educational program on prevention of such infections to determine the effectiveness of the program. Results of surveys in which the questionnaire is used can lead to better educational programs for critical care nurses in infections associated with use of CVCs.

2.2. European ICU nurses' knowledge of evidence-based CVC-RI prevention

Based on the article: Labeau SO, Vandijck DM, Rello J, Adam S, Rosa A, Wenisch C, Bäckman C, Agbaht K, Csomos A, Seha M, Dimopoulos G, Vandewoude K, Blot S, for the EVIDENCE-study investigators. Centers for Disease Control and Prevention guidelines for preventing central venous catheter-related infection: Results of a knowledge test among 3405 European intensive care nurses. Crit Care Med. 2009;37(1):320-323.

Introduction

Central venous catheters (CVCs) are life-sustaining devices, but carry a substantial infection risk.[344] Catheter-related infections represent 10-20% of all nosocomial infections.[344] The median rate of central line-associated bloodstream infection in ICUs of all types ranges from 1.6 to 6.8 per 1000 catheter-days.[345] Evidence-based prevention guidelines are available,[14] but as far as we know, clinicians' knowledge of these recommendations has not been assessed by means of a validated test.

This study is part of the EVIDENCE-project, that aims to develop an e-learning platform on infection prevention for ICU nurses (URL: www.vvizv.be/Pages/Evidence.php). As part of the needs analysis that precedes its development, European ICU nurses' knowledge of evidence-based guidelines for infection prevention is assessed using validated questionnaires.[293, 294, 333]

This paper reports the results of 3405 European ICU nurses on a knowledge test concerning the guidelines for preventing central venous catheter-related infection (CVC-RI) from the Centers for Disease Control and Prevention (CDC)

Methods

We conducted a survey, using a validated and reliable multiple-choice knowledge test,[294] based on the CDC central venous catheter-related infection prevention guidelines (Table 14).[14] To establish a European network, 31 potential collaborators were identified by searching the electronic database *Pubmed* for researchers with a particular interest in ICU infections. They were invited to act as a national representative beginning of October 2006. Representatives engaged to distribute the questionnaire nationally among ICU nurses, and to return the filled out copies via postal mail by March 1, 2007. Of 31 potential collaborators contacted, 26 agreed to cooperate and were mailed the questionnaire mid October 2006.

Table 14: Nurses' answers on ten multiple choice questions

Item		% of answers
1. It is recommended to replace CVCs routinely …		
A	Yes, every seven days	24.6
B	Yes, every three weeks	16.0
C *	No, only when indicated	55.8
D	I do not know	3.6
2. It is recommended to replace CVCs over a guidewire …		
A	Yes, every three days	3.8
B	Yes, every seven days	7.4
C *	No, only when indicated	74.5
D	I do not know	14.3
3. It is recommended to replace pressure transducers and tubing routinely …		
A *	Yes, every four days	53.1
B	Yes, every eight days	15.8
C	No, only when indicated	22.5
D	I do not know	8.6
4. In settings with a high rate of catheter-related infections it is recommended to use a CVC coated or impregnated with an antiseptic agent …		
A *	Yes, in patients whose CVC is expected to remain in place for more than five days	30.9
B	No, because the use of such catheters is not cost-effective	7.0
C	No, because the use of such catheters does not result in a significant decrease in the rate of catheter-related infections	26.1
D	I do not know	36.0
5. It is recommended to change the dressing on the catheter insertion site …		
A	On a daily basis	31.7
B	Every three days	22.9
C *	When indicated (soiled, loosened, …) and at least weekly	43.4
D	I do not know	2.0
6. It is recommended to cover up the catheter insertion site with …		
A	Polyurethane dressing (transparent, semipermeable)	62.6
B	Gauze dressing	8.2
C *	Both are recommended because the type of dressing does not affect the risk for catheter-related infections	26.2
D	I do not know	3.1
7. It is recommended to disinfect the catheter insertion site with …		
A *	2% aqueous chlorhexidine	13.9
B	0.5% alcoholic chlorhexidine	42.5
C	10% povidone-iodine	33.1
D	I do not know	10.5
8. It is recommended to apply an antibiotic ointment at the insertion site of a CVC …		
A	Yes, because it decreases the risk for catheter-related infections	5.8
B *	No, because it causes antibiotic resistance	29.6
C	No, because it does not decrease the risk for catheter-related infections	47.8
D	I do not know	16.8
9. When lipid emulsions are administered through a CVC it is recommended to replace the administration set …		
A *	Within 24 hours	90.0
B	Every 72 hours	5.9
C	Every 96 hours	0.9
D	I do not know	3.2
10. When neither lipid emulsions, nor blood products are administered through a CVC it is recommended to replace the administration set …		
A	Every 24 hours	28.6
B	Every 48 hours	38.5
C *	Every 96 hours	26.5
D	I do not know	6.4

*: correct answer according to CDC guidelines;
CVC: central venous catheter

They instructed local nurses through responsible hospital staff. Monthly newsletters strengthened the network.

The questionnaire comprised ten questions; each correct answer was given one point; a wrong answer did not affect the score negatively. A maximal score thus consisted of ten points, a minimal score of zero points.

Demographics included nationality, gender, ICU experience, number of ICU beds, and acquisition of a post-graduate degree in intensive care, provided by a higher education institution or similarly professionally accredited organisation.

Statistical analysis was performed using SPSS for Windows 13.0.0 (SPSS, Chicago, IL, US). Continuous variables are described as median (interquartile range). Chi-square, Mann-Whitney U and Kruskal-Wallis tests were used as appropriate. Relationships between total scores and demographics were assessed by linear regression analysis. Variables with $p>0.15$ were stepwise removed from the regression model.

The study was reviewed and approved by the Ethics Committee of Ghent University Hospital.

Results

Data were obtained by 22 of 26 countries that had agreed to cooperate. Belgium provided 762 questionnaires (22.4%), Portugal 484 (14.2%), Austria 204 (6.0%), Turkey 197 (5.8%), Hungary 178 (5.2%), Switzerland 178 (5.2%), Greece 175 (5.1%), Sweden 147 (4.3%), Spain 143 (4.2%), Italy 140 (4.1%), Germany 138 (4.1%), Finland 121 (3.5%), Slovenia 120 (3.5%), Slovakia 112 (3.3%), The Netherlands 93 (2.7%), Latvia 82 (2.4%), Malta 43 (1.3%), Denmark 31 (0.9%), Norway 16 (0.5%), United Kingdom 15 (0.4%), Czech Republic 15 (0.4%), and Lithuania provided 11 questionnaires (0.3%). Overall, 3405 questionnaires (response rate 70.9%) were collected. Table 14 shows the questionnaire and nurses' answers. Table 15 demonstrates the scores according to the demographics.

The mean score was 4.44 on 10 questions. Experienced nurses performed significantly better than less experienced nurses ($p<0.001$ for <1 year vs. >1 year; $p<0.001$ for <5 years vs. >5 years; and $p=0.002$ for <10 years vs. >10 years ICU experience, respectively). Nurses from larger ICUs scored significantly lower than nurses from smaller units ($p<0.001$ for <8 vs. >8 beds and for <15 vs. >15 beds, respectively).

Table 15: Answers according to respondents' characteristics

Characteristic	Mean	Median (interquartile range)	*p*
Total cohort (n = 3405)	4.44	4 (3 – 5)	-
Gender			0.094
Female (n = 2741)	4.42	4 (3 – 5)	
Male (n = 664)	4.52	5 (4 – 6)	
Number of ICU beds			< 0.001
<8 beds (n = 1003)	4.73	5 (4 – 6)	
8 – 15 beds (n=1406)	4.39	4 (3 – 5)	
>15 beds (n =972)	4.21	4 (3 – 5)	
Years of ICU experience			< 0.001
<1 year (n=392)	3.96	4 (3– 5)	
1 – 5 year (n = 997)	4.42	4 (3 – 5)	
6 – 10 years (n = 708)	4.52	5 (4 – 5)	
>10 years (n = 1300)	4.55	5 (4 – 5)	
Qualification in intensive care			0.205*
Yes (n = 1380)	4.43	4 (3 – 5)	
No (n = 1075)	4.44	4 (3 – 5)	

* only taking in account participating countries where such a degree can be obtained (Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Hungary, Italy, the Netherlands, Norway, Slovakia, Slovenia, Spain, Sweden, Switzerland and the United Kingdom). The total number of respondents from these countries is 2467. Numbers may not always add up to 3405 due to missing values.

Linear regression analysis (R^2=0.028) showed ICU experience (per class of increase: <1, 1-5, 6-10, or >10 years of experience) to be independently associated with better test scores (p<0.001; B ± standard error 0.150 points ± 0.025; 95% confidence interval (CI) 0.101–0.199). An increase in class of the number ICU beds (<8, 8-15, or >15 beds) was associated with lower scores (p<0.001; B ± standard error -0.272 points ± 0.034; 95% CI -0.399 – -0.204).

Discussion

The Institute for Healthcare Improvement (IHI) has issued a *Central Line Bundle* [346] to raise clinicians' awareness of recommendations for central venous catheter-related infection prevention. Use of the bundle is promoted as part of the 5 Million Lives Campaign, aiming to improve American healthcare's quality by protecting patients from five million incidents of medical harm between December 2006 and December 2008.[347] Indeed, awareness is a *conditio sine qua non* for guideline implementation. We are convinced that thorough understanding of the recommended strategies is a first step in overcoming potential barriers to compliance, and a significant contribution to the improvement of patients' safety.

Although our questionnaire evaluated knowledge, we assume that our results, at least to a certain extent, also reflect nursing practice. Generally, a varied distribution of answers among the different response alternatives is shown. This accords with the findings of a

survey on practices involving catheter care, that reported a wide diversity of practice and a lack of consistent adherence to the CDC guidelines.[289]

As care for the catheter insertion site typically is a nursing responsibility, it could be assumed that questions about this topic would mainly be answered correctly. This assumption proved to be wrong. Lobo et al.[41] reported similar results with 40% of medical residents being unable to answer correctly on a question concerning skin preparation for CVC insertion. The fact that 33% of nurses think that it is recommended to disinfect the catheter insertion site with 10% povidone-iodine can result in a higher incidence of catheter-related infection, for in a randomised trial the use of 2% aqueous chlorhexidine was associated with lower incidence of local catheter-related infection and catheter-related bacteraemia than 10% povidone-iodine or 70% alcohol.[348] Nevertheless, although the CDC guidelines recommend using 2% chlorhexidine, they also state that tincture of iodine, an iodophor, or 70% alcohol can be used as well.[14] This lack of an unambiguous recommendation is not only reflected by the variety in response alternatives chosen by our respondents, but also by various investigators' continued search for the most effective disinfection solution for catheter care.[153]

Both sterile gauze and transparent, semi-permeable dressings can be recommended to cover the catheter site.[14] Interestingly, a majority (62.6%) thinks that polyurethane dressings are recommended while 8.2% indicates gauze dressings as the recommended dressing type. It can be assumed that these answers reflect practice and nurses' preferences: in a survey by Rickard et al.[289] nurses reported a predominant use (93%) of semi-permeable transparent dressings, with utilisation of gauze dressings reported by only 7%. Transparent dressings have many advantages, but gauze dressings can be preferred if blood is oozing from the insertion site or in settings where the more expensive polyurethane dressings are unavailable.

Nurses seem convinced of an excessive need to change devices: dressings at the catheter site as well as administration sets are replaced too frequently. It has nevertheless been demonstrated that frequent changes of these devices do not decrease the risk of catheter infection, while they increase the assistance cost.[349-354] Moreover, frequent changes may have a negative impact on patients' comfort.

A large number (36.0%) of respondents do not know what is recommended concerning the use of coated central venous catheters. This unawareness presumably reflects an infrequent use of these devices, whose role in preventing infection is still being defined.[355] Moreover, contrarily to the CDC guidelines that recommend the use of antimicrobial catheters under special circumstances, the German guidelines consider this as an unresolved issue.[153] Indeed, and as a first limitation of our study, CDC recommendations may not always accord with the participating countries' national guidelines. Nurses may have answered according to national/local rather than international guidelines. As a consequence, besides a lack of knowledge or deficiencies in training, the poor test scores may reflect differences in what is regarded as good practice, and/or a lack of consistent policy. Developing pan-European guidelines would help to rationalize conflicting recommendations.

Further, and as with all surveys, our results may suffer from selection bias. Possibly, our respondents were more motivated or more interested in infection prevention than non-responders. If so, the scores of non-responders might even be lower than those reported.

Furthermore, from some countries a rather small number of questionnaires was collected (e.g. Lithuania, United Kingdom). Results from these countries may be less representative than those from countries where a larger number of questionnaires were gathered. Also, although the questionnaire has been validated before use, the phrasing of question five, concerning the frequency of change in catheter dressings, can induce to misunderstanding because the CDC guidelines recommend replacing gauze dressings every 2 days and transparent dressing at least every 7 days. Rephrasing this questions should be considered before further use of the survey tool. Last, our questionnaire linked no weights to the different strategies' relative importance, nor were any costs taken into account.

The major strength of our study is the large sample size and the amount of participating countries.

In conclusion, there is room for improving European ICU nurses' knowledge of CVC-RI prevention guidelines. We recommend including supplementary support from current evidence-based guidelines in their educational curricula and continuing refresher programs.

3. Knowledge about evidence-based guidelines for the prevention of surgical site infection

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Introduction

Worldwide, healthcare-associated infection (HAI) constitutes a major public health problem. Prevalence rates of 5% to 9% and 5% to 10%, respectively, are reported in European[47] and American[1] acute hospital settings. In developing countries, the risk of infection is 2 to 20 times higher, with a proportion of patients infected that can exceed 25%.[356] Serious complications caused by HAI include increased morbidity and mortality and substantial added costs.[13] Complications can afflict all patients, but those requiring intensive care particularly are at risk.[262] The significant physical, social, and psychological outcomes for the patients and their relatives have increased both government and public awareness of the risks associated with healthcare interventions, especially that of acquisition of new infections.[9] In the United States, a number of states have enacted legislation to mandate public reporting of HAI, and additional states continue to propose similar legislation.

Surgical site infections (SSI) account for one-fourth of all HAIs.[20] Approximately 500,000 SSIs occur annually in the United States, resulting in 3.7 million excess hospital days and $1.6 billion in extra hospital charges.[357] In general surgery, the incidence varies between 2% to 3% and 12% to 15%, depending on the class of operation.[25]

Nurses are in an excellent position to participate, or play a leading role in initiatives that aim to minimize the risk of SSI, and thus to enhance patient safety. The reliable implementation of peri-operative evidence-based guidelines for the prevention of SSI and SSI-related deaths was a goal of the Institute of Healthcare Improvement's (IHI) 100,000 Lives and subsequent 5 Million Lives Campaign (http://www.ihi.org). The IHI website reports many success stories in which nurses took the lead to realize extraordinary progress in quality of care and patient safety. Indeed, many SSIs are preventable,[67] and evidence-based guidelines are readily available to guide healthcare professionals in daily practice.[3, 13, 20] However, clinicians' adherence to SSI guidelines is known to be suboptimal.[25] Education of healthcare

professionals, preferably as part of a multifaceted quality program, has been shown to promote guideline implementation and HAI reduction.[149]

To promote knowledge of evidence-based recommendations for infection prevention among intensive care unit (ICU) nurses, we conceived a European study, called EVIDENCE, that aimed to develop a website-based interactive e-learning module on infection prevention and infection control (URL: www.evidenceproject.org). As the first step in any educational endeavour is needs analysis,[330] we started the project by assessing our target group's knowledge of evidence-based measures for infection prevention. For this purpose, we developed a multiple choice knowledge test concerning the evidence-based measures for preventing ventilator-associated pneumonia and a second one concerning the prevention of central venous catheter-related infection.[293, 294] Subsequently, we used these questionnaires to assess the knowledge of over 3300 European ICU nurses . The overall results of these tests were rather poor[296, 297, 333] and indicated that substantial opportunities exist to optimize European ICU nurses' knowledge of both topics.

The current manuscript reports on the development and validation of a similar multiple choice questionnaire concerning the prevention of SSI, and the results of a survey using this questionnaire among a sample of 650 Flemish ICU nurses.

Methods

Design

We conducted a cross-sectional questionnaire survey using a multiple choice knowledge test. The survey was preceded by experts' assessment of face and content validity and reliability testing of the questionnaire. The study was approved by the Ethics Committee of Ghent University Hospital.

Instrument Development

We developed a multiple choice questionnaire (Table 16), based on the CDC SSI prevention guideline,[20] with 4 response alternatives per question: one correct answer, two distractors, and the option "I do not know" to discourage guessing. The demographics gathered included gender, years of experience in ICU nursing (<1 year; 1 - 5 years; 6 - 10 years or >10 years), number of ICU beds in the hospital of employment (<8 beds, 8 - 15 beds, >15 beds), and whether nurses had a specialized qualification in emergency and intensive care.

Table 16: Questionnaire and results of the item analysis

		D	Q	DV	% of answers
1. It is recommended to protect a primarily closed incision …				0.32	
A	during the first 12 hours following surgery;		0.2		15.08
B*	during the first 24-48 hours following surgery;	0.5			45.54
C	during the first 5 days after surgery;		0.2		35.08
D	I do not know.		0.0		4.00
2. The appropriate time to shower or bathe with an uncovered incision is …				0.34	
A	≥ 48 hours following surgery;		0.1		7.23
B	≥ 96 hours following surgery;		0.2		18.00
C*	unresolved by lack of evidence;	0.4			39.38
D	I do not know.		0.4		35.23
3. Surveillance succeeds in reducing the incidence of SSI.				0.41	
A*	Yes it does, and without supplementary preventive measures.	0.1			10.46
B	Yes it does, but only when accompanied by supplementary preventive measures.		0.4		40.77
C	No it does not, surveillance only helps to gain insight into the prevalence of infection, but has no influence on incidence rates.		0.4		36.77
D	I do not know.		0.1		12.0
4. Elective surgery on patients with remote site infections should be postponed until the infection has resolved.				0.27	
A*	This is true for all patients.	0.3			34.77
B	This is only true for debilitated patients.		0.3		28.38
C	This is only true for patients infected with multi-resistant microorganisms.		0.2		20.15
D	I do not know.		0.2		16.23
5. SSIs are classified as …				0.50	
A*	superficial incisional SSI, deep incisional SSI, and organ/space SSI;	0.1			6.8
B	superficial incisional SSI, SSI in subcutaneous to fascial layers, and subfascial SSI;		0.2		19.5
C	superficial incisional SSI, deep incisional SSI, and necrotising SSI;		0.5		54.4
D	I do not know.		0.2		19.3
6. Stitch abscesses (minimal inflammation and discharge confined to the points of suture penetration) are classified as SSI.				0.34	
A	This is true.		0.2		21.23
B*	This is false.	0.5			46.15
C	This is only true when the patient simultaneously has fever.		0.3		26.00
D	I do not know.		0.1		6.46
7. To be classified as SSI, a superficial incisional infection needs to occur …				0.53	
A	within 7 days;		0.7		69.92
B	within 15 days;		0.1		6.92
C*	within 30 days;	0.02			2.31
D	I do not know.		0.2		21.54
8. If the patient's hair at or around the incision site interferes with the operation, it is recommended to remove it by …				0.31	
A	razor shave;		0.3		28.00
B	depilatory agents;		0.2		16.15
C*	electric clippers;	0.5			49.85
D	I do not know.		0.1		5.85
9.The recommended time of pre-operative hair removal in elective surgery is …				0.38	
A*	immediately before surgery;	0.3			25.85
B	≤ 12 hours before surgery;		0.1		42.77
C	unresolved by lack of evidence;		0.2		20.15
D	I do not know.		0.1		11.08

SSI: surgical site infection

*: correct answer

D: Difficulty of the item; Q: Quality of the option; DV: Discriminative value

In Belgium, this qualification can be achieved after the three years of basic nursing education (bachelor degree) and is acknowledged as a bachelor-after-bachelor degree.

Expert validation

The questionnaire was presented to seven experts to assess face and content validity. All experts had at least a master's degree in nursing or medical-social sciences, and were, at least locally, involved in research on ICU acquired infections with special interest in SSI. In order to achieve face validity, experts were asked if all questions were clearly worded and would not be misinterpreted. For content validity, the experts evaluated the nursing relevance of the 10 items by using a scale of 1 to 3, where 1 = not relevant, 2 = relevant but not necessary, and 3 = absolutely necessary. Additionally, they were asked if, according to them, important issues that were relevant for our target group were lacking. Per item, an Index of Content Validity (CVI) was calculated,[315] that reflects the proportion of consulted experts agreeing on the content validity of an item. When six or more experts are consulted, one or more can be in disagreement with the others while content validity is still established beyond the 0.05 level of significance. When seven experts are used, endorsement of at least five is needed.

Item analysis

Revising tests on the basis of their scores, is an essential part of improving instruction.[314] Therefore, the difficulty level and the discriminative value of the items of the questionnaire were analysed. The quality of the response alternatives was also assessed.[314, 316, 317]

a) Difficulty level

The difficulty level of a question is defined as the proportion of respondents who answer the question correctly.[314, 316, 317] Possible values range from 0.0 to 1.0. Items that are answered correctly by more than 90% of the respondents (value >0.9) are considered to be too easy; items answered correctly by less than 10% of the respondents (value <0.1) are considered to be too difficult.

b) Item discrimination

The discriminative value indicates how well a question distinguishes between high-scorers and low-scorers.[314, 316, 317] For calculating the discriminative value of each item, the

respondents were divided into a 27% group of high-scorers and a 27% group of low-scorers. Then, the following formula was used:

$$\frac{\text{number of correct answers in 'high' group} - \text{number of correct answers in 'low' group}}{\text{total number in both groups}}$$

Values ranging 0.35 and higher are (very) good values; values ranging 0.25 to 0.35 are satisfying to good; values 0.15 to 0.25 are mediocre to satisfying; and values less than 0.15 are bad to mediocre.[358, 359]

c) Quality of the response alternatives

The quality of a response alternative is defined by the proportion of respondents who choose the alternative. Values range from 0.0 to 1.0.[314, 316, 317] Response alternatives with a value 0.0 are not attractive, and those with a value 1.0 might be too attractive.

Sample

The questionnaire was distributed among all 809 participants of the Flemish Society for Critical Care Nurses' annual congress (Ghent, Belgium, 23 November 2007). These participants are nurses who work in ICUs in the whole of Flanders.

Procedure

A copy of the questionnaire was pre-included in every congress bag, and bags were handed to the participants when entering the congress hall. After the chairman's introductory speech, a board member of the Society presented the questionnaire in a plenary session. All participants were invited to participate in the survey, and were asked to answer to the questions individually. Each question was read aloud and simultaneously projected in the congress hall with a 30-second time interval to write down answers between two questions. Then, all copies were collected immediately and anonymously.

Statistical analyses

Continuous variables are described as median (interquartile range). Chi-square test, Mann-Whitney U test and Kruskal-Wallis test were used as appropriate. Relationships between total scores and demographic data were assessed using linear regression analysis. Statistical analysis was performed using SPSS for Windows 13.0.0 (SPSS, Chicago, IL, US). Two-tailed $p<0.05$ was considered statistically significant.

Results

Expert validation

The remarks of the expert panel were collected and discussed. The first version of the questionnaire contained ten questions. One question concerned the issue of pre-operative bowel preparation, which was identified by the experts as overruled by more recent evidence. This question was deleted from the questionnaire and minor revisions of the wording of some other questions were performed. The experts considered all nine remaining items of the questionnaire relevant for nursing practice. Calculation of the CVI reflected their unanimous agreement with the questionnaire's content and clarity. The final questionnaire is shown in Table 16.

Item analysis

The results of the item analysis are integrated in Table 16.

Overall values for item difficulty ranged from good to very good. Only for question seven (time frame in which a superficial incisional infection needs to occur to be classified as SSI), a very low value (0.02) was noted, indicating that only 2% of the nurses answered correctly.

Values indicating the quality of the response alternatives ranged from 0.1 to 0.7, thus demonstrating a good overall quality. Moreover, the standard response alternative "I do not know" was selected by at least 10% of the sample in all questions but the first, suggesting that this phrase succeeded in discouraging the nurses from guessing. With values ranging between 0.27 and 0.53, all questions show to discriminate adequately between low scorers and high scorers in a good to very good way.

Survey

Of the 809 registered participants, 650 completed questionnaires were available for analysis (response rate: 80.3%). The mean test score was 2.61 on 9 questions (29%). Forty-five% of nurses knew that primarily closed incisions must be protected for 24 to 48 hours, and 39% that the appropriate time to shower or bathe with uncovered incisions is unresolved. Only 10% knew that postoperative surveillance by itself succeeds in reducing the incidence of SSI, and 35% that elective operations on patients with remote site infections should be postponed until the infection has resolved. The correct classification of SSI was known by 7% only, while 46% knew that stitch abscesses are not to be reported as SSI. Only 2% recognized

the exact time frame in which emerging superficial incisional infections are classified as SSI. Twenty-six% knew that preoperative hair removal should take place immediately before surgery, and 50% knew that electric clippers are recommended.

Table 16 shows the distribution of the nurses' answers among the response alternatives. In Table 17, the demographics of the sample are shown, along with the test scores according to these characteristics.

Table 17: Scores on nine questions according to respondents' characteristics

Characteristic	n	Mean (%)	Median (interquartile range)	*p*
Total cohort	650	2.61 (29.00)	3 [2 – 4]	-
Gender				0.001
Female	169	2.50 (27.77)	2 [2 – 3]	
Male	478	2.92 (32.44)	3 [2 – 4]	
Missing	3			
Number of ICU beds				0.066
<8 beds	92	2.39 (26.55)	2 [1 – 3]	
8 – 15 beds	171	2.76 (30.66)	3 [2 – 4]	
>15 beds	328	2.61 (29.00)	2 [2 – 4]	
Missing	59			
Years of ICU experience				0.202
<1 year	52	2.56 (28.4)	2,5 [1 – 4]	
1 – 5 year	158	2.77 (30.77)	3 [2 – 4]	
6 – 10 years	119	2.44 (27.11)	2 [1,5 – 3]	
>10 years	314	2.63 (29.22)	2 [2 – 4]	
Missing	7			
Specialised qualification				0.892
Yes	501	2.61 (29.00)	3 [2 – 4]	
No	133	2.61 (29.00)	2.5 [2 – 3]	
Missing	16			

ICU: intensive care unit

Univariate analysis showed that male nurses performed significantly better than their female colleagues (p<0.001). Linear regression analysis (adjusted R^2 = 0.02) identified male, as compared to female gender, to be independently associated with better test scores (p<0.001; B ± standard error 0.51 points ± 0.12; 95% confidence interval 0.27 – 0.75). No significant differences in scores were found between other subgroups.

Discussion and Limitations

We evaluated knowledge of the evidence-based CDC recommendations[20] for preventing SSI among 650 ICU nurses using a custom designed knowledge test. The questionnaire demonstrates face and content validity, and was shown to be reliable. The overall scores

were poor, thereby representing a significant obstacle to comply with guidelines. Also, as the answers of nurses who are unfamiliar with the guideline most probably reflect their daily practice, a substantial opportunity for improving SSI prevention seems to exist.

Our sample consisted of intensive care nurses because they were the target group for whom, within the EVIDENCE-project, our e-learning module on infection prevention will be developed and whose educational needs we are analysing. Nurses who care for surgical ICU patients may be better aware of the evidence-based prevention recommendations than nurses who work in medical units, but as we did not ask our respondents in which type of ICU they worked, our findings cannot clarify this issue. Nevertheless, surgical patients are not exclusively found in the surgical ICU, and SSI prevention is assumed to be common knowledge among all nurses. In Flanders, surgical nursing care is included in the second of the three years basic nursing education (professional bachelor degree). As such, pre-operative and postoperative SSI prevention strategies are considered common knowledge among nurses. Also, the questions of our survey were restricted to issues concerning pre-operative and postoperative nursing care, while measures that concern patient care in the operating theatre were not taken into account. The reason for this selection was that the nursing tasks and responsibilities in the operating theatre are far too specific to be commonly known among nurses who do not work in this specific setting.

The distribution of the answers among the response alternatives demonstrated that misconceptions concerning the correct measures to prevent SSI abound. First, only 10% of the nurses were aware of the fact that surveillance succeeds in reducing the incidence of SSI without supplementary preventive measures, while both answering options that were not the correct answer scored approximately 40% of responses. Also, more than half of the sample (54%) wrongly classified SSIs in superficial incisional SSI, deep incisional SSI, and necrotising SSI, while the correct classification was only checked by 7%. Moreover, it was commonly (by 70%) but falsely thought that superficial incisional infections need to occur within 7 days following surgery to be classified as SSI, while 30 postoperative days is the correct time frame (2% only). Mapping out these kinds of misconceptions is important for understanding and meeting nurses' specific educational needs.

At the time of our investigation, the 1999 CDC guideline[20] was the most recent directive for evidence-based SSI prevention measures. Recently, the Infectious Diseases Society of

America (IDSA) and the Society for Hospital Epidemiology of America (SHEA) jointly issued a compendium of strategies to prevent healthcare-associated infections,[3] including a practice recommendation for SSI prevention,[89] on the basis of a review of previously published guidelines and studies published after the existing guidelines. The British National Institute for Health and Clinical Excellence (NICE), however, also recently released a SSI prevention guideline,[13] that differs from the CDC[20] and IDSA/SHEA[89] recommendations concerning the time frames for pre-operative hair removal and postoperative showering or bathing, respectively. Whereas the CDC recommend hair removal immediately before surgery,[20] NICE broaden this time frame to the day of surgery.[13] Also, whereas the CDC consider the time to shower or bath postoperatively an unresolved issue,[20] NICE state that patients can shower safely 48 hours after surgery.[13] By developing one encompassing, uniform guideline, controversies and contradictions between published recommendations could be addressed.

Contrasting recommendations for identical interventions may induce confusion and uncertainty among healthcare professionals, thus hampering guideline adherence. However, it remains questionable whether a universal guideline would enhance implementation. Recently it was suggested to simultaneously implement several practice improvements in order to obtain a potential synergy between combinations of interventions.[1] In this context, use of the World Health Organisation's (WHO) Surgical Safety Checklist, which was developed within the framework of the WHO Safe Surgery Saves Lives Campaign (http://www.who.int/patientsafety/safesurgery/en/), has been shown to significantly reduce patient complications (from 11% to 7%) and prevent deaths (1.5% to 0.8%) in a study that was conducted in eight locations worldwide.[360] Combined use of this checklist in the operating theatre and educational initiatives concerning preoperative and postoperative SSI prevention strategies for bedside nurses could offer an opportunity for nurses to contribute to a substantial reduction of infection and an enhancement of patient safety.

To the best of our knowledge, our study was the first to evaluate nurses' knowledge of SSI evidence-based prevention guidelines by means of a validated knowledge test. When interpreting our study results, a number of limitations should nevertheless be taken into account. Our sample consisted of nurses attending the annual congress of the Flemish Society of Critical Care Nurses. This convenience sampling may have led to including more motivated nurses, and thus better results. Therefore, our results cannot be extrapolated.

This selection bias may be limited by the fact that Belgian federal legislation obliges all ICU nurses who hold a specialized qualification in intensive care to attend at least 16 hours a year of continuing education to maintain this qualification. Moreover, our sample size is quite substantial and accounts for as many as 20% of all Flemish ICU nurses.

Finally, guidelines can change over time. Adaptation and re-evaluation of the questionnaire will be needed every time new evidence for the prevention of SSI will be published.

Conclusion

A reliable questionnaire that has face and content validity was developed to assess intensive care nurses' knowledge of evidence-based strategies for the prevention of SSI. Results of surveys using this questionnaire can be used to focus educational SSI prevention programs. The survey we conducted demonstrated that there is substantial room for improving Flemish ICU nurses' knowledge of SSI prevention. Current guidelines should support their schooling and continuing education.

Conclusion of part two

The needs analysis reported in part two of this thesis based performed by means of self-developed multiple choice questionnaires.
For all questionnaires, a first requirement for items to be included was that they had to consist of interventions of which the effectiveness had been investigated, and of which the results had been published at the time of questionnaire development. As our focus was on the promotion of evidence-based prevention practices, the correct answers on the questions in the knowledge tests were directly based on the then most recent evidence-based guidelines. This nevertheless caused us to restrict ourselves in the possibility of creating questions. Besides the focus on promoting evidence-based infection prevention practices, our choice had the underlying rationale that an undeniable proof should be available to demonstrate that all questions only had one single correct answer.

An important limitation of our questionnaires, which is inherent to knowledge tests as such, and in particular to our questionnaires due to our choice to develop only questions that were strictly based upon evidence-based guidelines, is that their value diminishes substantially as soon as new knowledge, c.q. evidence, becomes available. In order to keep them up to date, they are constantly to be adapted to the latest evidence, followed by new validation processes.

Additionally, the questionnaires could be submitted to additional validation procedures.
Construct validity has not been assessed for any of the questionnaires. Construct validity indicates what construct a test actually measures and can be established using the known-groups technique. In this procedure, groups that are expected to differ on the critical attribute take the test, and group scores are compared. In order to establish construct validity for our questionnaires, they had to be submitted to a group of other than critical care nurses. The scores of the non-critical care nurses should then have differed from those of a group of critical care nurses. Prevention of central venous catheter-related infection and surgical site infection, however, are topics that are to be considered as required common knowledge among all nurses, regardless their professional specialty, for central venous catheter-related infections and surgical site infections are not exclusively and specifically

ICU-related infections. Moreover, in Flanders, both nursing care for central venous catheters and wounds are included in the curriculum of the three basic years of nursing education. As for the questionnaire on the prevention of ventilator-associated pneumonia, the known-groups technique could have been applied to assess construct validity as the care for ventilated patients is predominantly an ICU-specific issue. This additional procedure could have added to the validity of the questionnaire.

As for the reliability testing of all three questionnaires, the method of item analysis was applied, which, to the best of our information, is the most suitable technique to assess the reliability of knowledge tests.

In a pilot testing of the questionnaire related to the prevention of ventilator-associated pneumonia, which was the first questionnaire we developed, we attempted to assess the stability of the questionnaire by means of a test-retest procedure. We nevertheless soon realized that, by that procedure, we did not test the stability of the questionnaire but rather the stability of our respondents' knowledge. Knowledge is not a stable attribute, and can change markedly from day to day. As an example, nurses who had completed the questionnaire at the test-phase may have been triggered to look up information and thereby have gained considerable knowledge by the time the questionnaire was re-presented to them for retesting. The test-retest procedure is not an appropriate technique if knowledge tests are involved.

When we started to develop the questionnaires, we considered evaluating their internal consistency. Thereto, different methods are available, such as the determination of Cronbach's alpha, Kuder-Richardson 20 and split-half techniques.

As our questionnaires are no scales with different subscales or multiple traits, but straight-forward knowledge tests with a single set of closed questions, it is not appropriate to submit them to an analysis for Cronbach's alpha determination.

We did submit the CVC-RI questionnaire to a homogeneity test using Kuder-Richardson 20 (KR20), a special form of coefficient alpha that applies when the items are scored dichotomously as right or wrong. The KR20 value obtained revealed to be poor, thus suggesting limited homogeneity of the questionnaire. Nevertheless, several arguments are

available to discuss the impact of the low KR20 value obtained on the value of the questionnaire. First, we do believe that the low internal consistency is predominantly caused by the low variance in the respondent's test results. The mean test result of the respondents (n=762) was 4.52/10 (interquartile range 4-5) with a variance of 2.06. Therefore, the lack of variance in the (poor) test results could be considered the major factor responsible for the low internal consistency, rather than the lack of homogeneity of the items in the questionnaire. Second, KR20's value is strongly related to the amount of questions in the questionnaire: as the amount of questions in the questionnaire is quite limited (ten items), the chance of obtaining a low KR20 is substantial. Third and last, the questionnaire aims to evaluate ICU nurses' knowledge on evidence-based guidelines for the prevention of CVC-RI. This renders the questionnaire quite fixed and the choice of items to be included restricted. Other factors that might influence KR20 values, such as the number and the choice of the response alternatives and the appropriateness of the population surveyed, were taken into consideration. However, knowing that a KR20 is not stable over time, is influenced by the population surveyed and by the respondents' level of knowledge, and taking into account the fact that the questionnaire does not contain any subdivisions, we considered it justified to use the questionnaire as such. Additionally, we were strengthened by the fact that the items included had previously been acknowledged by a panel of content experts to cover the knowledge domain for this topic.

We did not test the internal consistency of the test by means of the split-half technique, in which a test is split in two halves, and in which the correlation between these two split halves is used to estimate the reliability of the test. This approach must be used when tests that measure more than one trait are being developed because items measuring each trait must be present in each half-test.[316] Our arguments for not submitting the questionnaires to this procedure are identical to those mentioned above.

In all our questionnaires items and distractors were treated equally: all correct answers scored one point and all distractors scored no points. Nevertheless, some items relate to issues for which the impact on the infection risk may be larger than others (e.g. the use of endotracheal tubes with extra lumen for the suction of subglottic secretions versus the choice between open or closed suction systems in the VAP prevention questionnaire), or to

issues in which the nurses' responsibility is larger than others (oral versus nasal intubation versus head of bed elevation in the VAP prevention questionnaire). Although it has been acknowledged that when comparing unweighted and weighted item scoring, the sets of scores are highly correlated, and that the differences between unweighted and weighted scores are small and usually observed in the upper and lower tails of the distribution of test scores,[314] the accuracy of test scores might have been improved by item weight attributions.

The results of our needs analysis clearly demonstrated low overall knowledge levels of evidence-based guidelines for the prevention of VAP, CVC-RI and SSI among European ICU nurses. Among 3405 European ICU nurses, the mean score on the 10-item test regarding the prevention of CVC-RI was 44%. The mean score obtained by 3329 European nurses on the 9-item VAP prevention questionnaire was 45%. The mean score on the questionnaire regarding the prevention of SSI among a sample of 650 Flemish ICU nurses was 29% only. These results led us to the conclusion that there was extensive room for an initiative aiming to enhance ICU nurses' level of knowledge regarding the topic of healthcare-associated infection.

Reflection about which resources could effectively and efficiently help to enhance ICU nurses' knowledge of infection prevention led to an extensive literature search on which resources would be helpful to address the educational needs of healthcare workers. This resulted in the finding that e-learning has recently been acknowledged to be an important educational tool, that allows distant learners to study wherever and whenever they prefer, and at their own pace.

Using open source software, a concise and interactive Web-based e-learning course that bundles the essentials on infection prevention in a comprehensible way was developed: the EVIDENCE *Crash Course*. Subsequently it was tested whether this course actually succeeds in increasing and sustaining knowledge among healthcare workers, as reported in Part three of this thesis.

PART THREE

E-LEARNING

"O this learning, what a thing it is!"

William Shakespeare (1564 - 1616)

The Taming of the Shrew, c. 1590-94

Introduction

Access to the right knowledge at the right time is a key factor for an effective and efficient healthcare system. Education of all members of the multidisciplinary team is therefore considered a first and crucial requirement when targeting implementation of interventions for infection prevention.[74] A shift of emphasis in education has been witnessed in the mid-nineties of the previous century from providing instruction to producing learning.[361] Critical thinking, independent and evidence-based learning, and feedback are since being regarded as indispensable features of this new learning paradigm.[362]

Quite simultaneously, a rise in the use of information technologies in (medical) education took a start. E-learning, a method which integrates information technology and the learning process by using material delivered through the internet,[363] was soon acknowledged to be a valuable educational tool.[364]

In order to help meeting the educational needs detected, the final step in the EVIDENCE-project consisted of the development and assessment of an e-course on the prevention of nosocomial infection in critically ill patients. Therefore, part three of this thesis is dedicated to the topic of e-learning.

The first chapter aims to introduce the reader to the concept of e-learning. As terminology used to describe Web-based learning, distance learning and e-learning is not standard, the chapter starts by outlining definitions. Next, a short historical overview is provided, aiming to elucidate the evolution of this recent educational resource over time into the concept it has become today. The first chapter is ended by listing the potential advantages and disadvantages associated with e-learning.

Chapter two offers a non-extensive overview of the literature concerning the value of e-learning in healthcare. After a general outline of the value of e-learning for healthcare professionals, the focus is on specific e-learning initiatives in the field of critical care, and infection prevention and control, respectively.

The third and last chapter of part three is dedicated to our own experiences with e-learning, as it relates on the development of the EVIDENCE *Crash Course*, and on the acquisition and retention of knowledge in healthcare workers who volunteered to studied the course.

1. The concept of e-learning

1.1. Definition

In its broadest sense, e-learning is the use of the Internet for education. When conducting a literature search, the terminology in respect of web-based or e-learning education is, however, not standard. Different terminologies have been used for online learning, which makes it difficult to develop a generic definition.[365] Besides e-learning, key words include Internet education, distance education, IT-learning, web-based education, web-based instruction and advanced distributed learning.[366]

In so-called *synchronous learning*, the educational content of Internet-based learning is provided at the same time as it is delivered from an instructor; in *asynchronous learning*, on the contrary, it is disconnected from the actual time of instruction and provided by tools such as recorded and saved audio, video, or text presentations.[367, 368] The separation of teacher and student in time and space clearly classifies web-learning as distance learning.[369]

Reime and colleagues describe e-learning as a method which integrates information technology and the learning process by using material delivered through the internet to create, foster, deliver and facilitate learning, anytime and anywhere.[363] In this thesis, the definition by Reime et al. has been used.

1.2. A brief history of e-learning

The seeds for distance learning have been sown as far back as the 1700s with the development of the first correspondence course. In England, in 1840, shorthand classes were being offered by correspondence courses through the mail, a method of distance learning that gained popularity in the early part of the last century.[369]

In the centuries to follow, new technologies made distance learning easier. Radio, television, video recorders, all made significant contributions. As an example, in 1953 the University of Houston offered the first televised college credit classes. Most courses aired at night so that students who worked during the day could watch them.

The genesis of e-learning as we know it today can be traced to the development of network communication in the late 1960's.[370] The invention of the World Wide Web, an internet-based hypermedia initiative for global information sharing, by Tim Berners-Lee in 1989 has

significantly impacted on distance learning.[371] These technological innovations introduced an unprecedented opportunity whereby people could communicate and collaborate despite differences in time and place. The first web-based course was developed in the United States of America in 1995.

Often, the early web-based courses were criticized for poor standards and lack of quality control methods as they relied almost exclusively on the learner's ability to read information and to use that information to answer questions.[369, 372] They have been gradually evolving over time and gaining in quality, following the evolution of the Internet through two phases, Web 1.0 and Web 2.0.

Web 1.0 is often described as the ‘‘read-only Web’’, as it provides a relatively passive experience for the user. Web 1.0 technology allows users to search and read texts, to watch and listen to multi-media files, and to interact with preprogrammed games and simulators. It can be considered to have begun in the year 1991 with the introduction of the Worldwide web and is stated to have ended in the year 2003, just before the era when Web 2.0 began.

Web 2.0 defines the more interactive and dynamic phase of the www. and is commonly referred to as the ‘‘read-write Web’’ for its concept of offering users a participatory platform. Hereby, users are able to generate Web site content, and to communicate interactively through wikis, blogs, podcasts, video-sharing, and social networking sites.

Both Web 1.0 and 2.0 thus incorporate various technologies that are commonly used in e-learning environments today.[368]

1.3. Advantages and disadvantages of e-learning

1.3.1. Advantages

More than anything else, flexibility appears to make e-learning attractive to learners.[373] Flexibility related to e-learning is multifaceted. First, different learning styles can be addressed and learning can be facilitated through mixed activities. Learners may also have the option to select study materials that meet their level of knowledge and interest. Moreover, self-paced learning modules allow learners to work at their own pace. They do not have to work faster to keep up with more advanced students or hold their pace to wait for struggling learners. They can review the material as many times as desired to enhance

their own understanding.[138] Thus, e-learning encourages students to take responsibility for their learning process.

Next, learners are not required to travel to attend classes. They can learn from the comfort of their own home or from any place where technical accommodations allow them to. The *just-in-time* nature of e-learning allows to study wherever access to a computer and the Internet is available. E-learning thus reduces travel-related costs and time.[138]

Healthcare professionals are expected to be computer and information literate at registration. As an additional asset, e-learning promotes the learners' development of computer and Internet skills, and of skills in time management.[363, 372, 374, 375]

Finally, e-learning contributes to methodological diversity and to changing the focus away from teaching to learning.[376]

From the point of view of the organisation, e-learning overcomes issues such as class room or instructor availability, staffs' combination of vacation schedules, current classes, or differing employee shifts. This can yield training that is accomplished more rapidly, while ensuring content consistency and standardization.[138] Also, organisations have the opportunity to provide educational materials tailored to the employees' specific needs.

Another benefit pertaining to the organisation is that, if desired, learners' activity is trackable. E-learning permits to log participants' actual course attendance, study time, test scores and study progress. This can be an important asset for healthcare settings where clinicians' activities for continuing education are (partially) funded, and therefore controlled, by the organisation.

A recent study assessed the economic sustainability of e-learning within a large scale via personnel work hour saving, and yielded positive results.[377] Costs associated with the development of e-modules will predominantly depend on the software used and the investment in personnel cost. In environments or economic climates with restricted resources for educational purposes, the use of open source software could prove to be highly advantageous.

1.3.2. Disadvantages

When using e-learning, unmotivated students or those with poor study habits may fall behind or experience difficulties in getting used to the lack of familiar structure and routine of conventional classes.[378] Also, learners may feel isolated or miss social interaction. Isolation of distance learners has been identified as a common reason for the high drop-out rate from online courses.[376] Also, if studying from home, potential distractors are numerous.

Particular student characteristics and factors that predict whether a student might drop out of or fail to achieve satisfactory results in e-learning courses include a lack of the course's clarity of design, of interaction with instructors, and of active discussion in the context of the course; a lack of self-motivation and the inability to structure one's own learning;[379] an absence of previous experience with distance learning, and enrolled hours, with students taking more hours being significantly more likely to complete a course.[380]

Technical barriers such as low performance computers or slow or unreliable Internet connections can be frustrating. Learners may experience a lack of technical support, can be hindered by (organisational) firewalls, or restricted available bandwidth.[376]

Finally, implementing e-learning in an organisation can be associated with high upfront costs, related to both personnel investment and technological requirements.

2. E-learning and healthcare

In past two decades, education for healthcare workers has witnessed a shift from one devoid of significant computer-based resources to that where such tools are regularly incorporated. Many nursing and medical students have reported e-learning to have been helpful toward their educational advancement.[367, 368, 381] The need for continual learning to enable professionals to maintain and develop their knowledge and skills to function effectively has greatly contributed to the ever-growing importance of e-learning for healthcare professionals.[368, 369]

2.1. The value of e-learning for healthcare professionals

With the rising use of Internet-based learning, various studies have attempted to evaluate its benefit for healthcare workers compared to no control or as part of a blended-learning model. A recent meta-analysis by Cook and colleagues[382] assessed the effect of Internet-based instruction for healthcare professionals compared to either no intervention or to non-Internet interventions. In total, 2193 studies were identified and 201 studies were included. Learners were students, postgraduate trainees, or health professionals in human or veterinary medicine, and the outcomes included learner satisfaction with the course, knowledge, clinical skills, and behaviors or effects on patients. In spite of the considerable heterogeneity in studies, this meta-analysis concluded that the strategies assessed in e-learning appeared to be more effective than no intervention –which is hardly surprising– but are likely similar in efficacy to traditional educational methods.[382] The authors recommended that further research should focus on the direct comparison of different Web-based interventions.

Another meta-analysis by Cook and colleagues[383] including 51 studies evaluating the effect of instructional design on learning outcomes among practicing and student physicians, nurses, pharmacists, dentists, and other health professionals. Internet-based interventions were compared with other Internet- or computer-based interventions and classified according to 22 different e-related instruction themes, including patient cases, games or simulation, interactivity, feedback, discussion, and audio. Although their findings were limited by methodological heterogeneity and small sample sizes, Internet-based resources incorporating features of interactivity, practice exercises, repetition, and feedback were associated with improvement in learning outcomes.

Cook and colleagues[384] sought also to answer how e-learning compares with non-computer instructional methods in time spent learning, and what features are associated with improved learning efficiency for health professionals. Their systematic review and meta-analysis included all studies published between 1990 and November 2008 investigating the use of the Internet to teach health professions learners in training or practice compared with another educational intervention. Health professionals included were students, postgraduate trainees, physicians, nurses, pharmacists, dentists, veterinarians, and physical therapists. Twenty eligible studies were identified. Random effects meta-analysis of eight studies comparing Internet-based with non-Internet-based instruction yielded a pooled effect size (ES) for time -0.10 (p=0.63) with positive numbers indicating a longer study time when use e-learning. Among comparisons of two e-learning interventions, providing feedback adds time (ES 0.67, p=0.003, two studies). Also, greater interactivity generally is associated with longer study time (ES 0.25, p=0.089, five studies). One study found that adapting to learner prior knowledge saves time without significantly affecting knowledge scores. Audio narration, video clips, interactive models, and animations were found to increase learning time but simultaneously facilitate higher knowledge and/or learners' satisfaction. Across all studies included, time correlated positively with knowledge outcomes (r=0.53, p=0.021). The authors concluded that, overall, e-learning and traditional educational interventions require similar study time.[384]

2.2. E-learning for critical care providers

Wolbrink and colleagues[368] conducted a MEDLINE/Pubmed systematic review from January 2000 to July 2011, aiming to investigate the suitability of e-learning for critical care providers. Working in a critical care environment requires an important amount of knowledge and a significant set of technical skills that need to be mastered. Besides, other key skills such as clinical decision making and teamwork need to be developed. Therefore, the authors are convinced that the benefit of simulating low volume, high-risk events and the appropriateness for the adult learner makes e-learning uniquely suited to healthcare professionals caring for the critically ill patient.

Six publications were identified assessing the use of e-learning specifically for critical care providers. These included the assessment of an online burn care module to medical students and interns in surgery and emergency medicine,[385] an online course to teach medical

students how to properly fill out a death certificate,[386] a Web-based intervention on recommended clinical guidelines for patients with acute respiratory distress syndrome,[387] an e-course on sterile technique for central venous catheter placement,[388] a difficult airway management course in anesthesia and internal medicine trainees,[52] and an avatar-based training to teach principles of crisis resource management to medical students and first-year residents in emergency medicine.[389]

The authors concluded that Web-based learning appears to be advantageous for the adult medical learner, especially in the field of critical care, if features such as interactivity, feedback and exercises are included. It was suggested that e-learning may become a vehicle for levelling of access to knowledge and information on the care of critically ill patients worldwide. Further work is esteemed necessary to develop a robust learning platform incorporating a variety of learning modalities for critical care providers.[368]

A concise review by Kleinpell and colleagues[390] aimed to identify, catalog, and critically evaluate Web-based resources for critical care education. As a result, an impressive list of over 135 tools specifically developed for ICU clinicians was generated, identifying a number of noteworthy educational websites and e-learning materials. All were meticulously reviewed to fulfill a set of stern requirements of quality and credibility. The authors concluded that e-learning today is being actively integrated into critical care medical and nursing training programs and for competency training purposes. Web-based resources are esteemed to help to serve as knowledge tools for educators, students, and clinicians. Although not objectively measured to date, it is suggested that awareness of available Web-based educational resources may enhance critical care practitioners' on-going learning and clinical competence.[390]

2.3. E-learning in the field of infection prevention and control

The impressive above-mentioned list of Web-based resources for critical care providers[390] was found to include only four tools related to the field of infectious diseases. Although of high quality, these sites mostly effectuate a passive transfer of knowledge, not possessing all components of a learning paradigm (critical thinking, independent learning, evidence-based learning, feedback). Moreover, they do not focus on infection prevention, but cover specialised topics mainly for advanced learners. Of all resources listed, only the Society for

Critical Care Medicine Infection Knowledge Line[391] appears to include a broad range of items, and addresses both beginners and advanced learners.

Besides for critical care providers, a number of local initiatives to integrate e-learning in the education of healthcare professionals concerning the prevention of infection has been reported on.

In Bergen, Norway, a college of nursing aimed to combine the development of a new curriculum with the enhancement of students' competences in cross-infection control. In collaboration with the Centre of Nosocomial Infection Control at the local hospital, they evaluated different approaches to acquiring and applying knowledge. In this context, Reime and colleagues[363] account on a newly developed e-learning program on infection control, normally used among employees in the hospital, which was evaluated in the setting of bachelor nurse students. The students were allocated to one group that used the e-learning program, or to another group that was given three hours-long traditional lectures. Both groups took a multiple choice test following their respective courses. Additionally, the students were divided into three focus groups to assess their experiences. The students were found to be satisfied with both teaching approaches. They rated the e-learning program as good on design and academic content, and found the integrated tests motivating. As for the results of the multiple choice test, the lecture group however had a higher sum score compared to the e-learning group ($p=0.01$). The authors concluded that e-learning and traditional lecturers both have to be regarded as equivalent educational resources. They underline the importance of students acquiring good computer skills as they will need to use these in clinical practice.[363]

Recently, Pellowe and colleagues[392] reported on the use of an e-learning project in the pre-registration nursing programme in the United Kingdom. The project was initiated by the National Health System (NHS) University and intended to be the definitive infection prevention programme for all NHS staff, both clinical and non-clinical. However, as lecturers at a higher education institution had been involved in the development of the programme, they saw its potential for use and trialled it among nurse students. The programme consisted of three parts. Parts 1 and 2 introduced the students to the topics of the problem of healthcare-associated infections; risk to patients; and how to protect patients and one's self. Part 3 provided more detailed information about the *EPIC* project, that resulted in the

development of national evidence-based guidelines for the prevention of healthcare associated Infections in the UK,[9] and included sections on hand hygiene; personal protective equipment; waste and sharps; and environmental cleanliness. The e-learning programme was embedded into a blended learning framework within the pre-registration nursing curriculum. To evaluate the e-learning programme, a short questionnaire was constructed using Likert-scale[343, 396] questions, and students were encouraged to complete the questionnaire online on completion of their learning experience.

Of the 495 students who had completed the programme, 57% filled out the questionnaire. Of these, 88% found it straightforward to register and access the programme; 91% were capable of easily selecting those sections they needed, and 62% reported no difficulty in working their way through the programme. Also, 84% of respondents were aware of their ability to revisit the programme at any time. As for the value of the programme, 88% of respondents reported having completed all mandatory sections of the e-learning course; 94% either strongly agreed or agreed having enjoyed this alternative form of learning. The relevance of the programme for their current education was acknowledged by 94%. Confidence in understanding the infection prevention topics studied was enhanced in 97% of students and 96% reported applying the knowledge gained to clinical practice.

The authors concluded that this e-learning infection prevention programme, although not originally intended for pre-registration nursing students, proved to be a useful additional resource in skills acquisition, especially when integrated into a blended learning framework. They esteem that this form of learning may become even more significant in nurse pre-registration programmes in the future.[392]

Another initiative to provide e-learning about infection control also emerged in the United Kingdom, where Desai and colleagues developed an Infection Control Training and Policies multimedia software package consisting of an introductory infection control training course and a hypertext version of a published book on infection control practices.[393] Various modules were integrated, including information on hospital-wide policies, policies for medical and surgical wards, special organisms, hospital support services, and staff and student health. The course was implemented at the local hospital and at three campuses of medical schools. Frequency of access to the software at the hospital wards was monitored; besides, a questionnaire survey was conducted among 25 ward-based users and 23 students

to assess perception and satisfaction. Additionally, medical students understanding of infection control was evaluated by inviting 52 third-year medical students attending an infection control lecture to answer a pre-training 30-item multiple choice questionnaire. Of them, 23 students, randomly chosen, were asked to undertake the e-course whilst the remaining 29 attended a lecture with the same content. Subsequently, both groups were invited to complete a 30-multiple choice questions post-training questionnaire.

During the first three months of the 18-month study period, the course was accessed 425, 319 and 349 times per month, respectively. Subsequently, access rates dropped to 100 – 150 per month. In a later phase of the study period, increased use by night-duty staff and at weekends was found. Of 23 medical students, only three reported not to enjoy using the software. Most users described the software as user friendly, and the three infection control staff involved in the ward-based assessment reported that the course covered all essential learning materials to introduce clinicians to infection control. While the evaluation of medical students' knowledge found no significant differences in the groups' pre-training scores, both forms of learning significantly increased students' knowledge levels, with an increase from 62.1% to 79.5% ($p<0.0001$) among students who took the traditional class, and from 63.5% to 83.4% ($p<0.0001$) among those who completed the e-course. No significant difference was found for the overall post-test scores between groups, but for nine questions regarding the chapter *Reducing the Risk* the e-course group scored significantly better (81.6%) compared with the traditional learning group (71.6%; $p=0.012$).
It was concluded that by implementing the e-course, evidence-based infection control practice information was been made readily available to staff and students in a new and acceptable format.[393]

Atack and Luke developed an online course in infection control in Ontario, Canada, to facilitate the delivery of standardised training to large numbers of health providers.[394, 395] The course was developed as a self-study course for workplace training and consisted of three modules: *Hand Hygiene*, *Routine Practices*, and *The Chain of Transmission*. The modules included text, photographs, video and graphics, as well as pre- and post-module knowledge tests and various exercises allowing students to self-evaluate their study progress. Twenty to 30 minutes of study time were required to complete one module.[395] Consequently, the authors examined the impact of the course on nurses' and allied

healthcare professionals' competency in infection prevention and control by means of Likert-scale[343, 396] pre- and post-intervention questionnaires.

Eighty-eight% (n=67) of the sample completed both the pre- and post-intervention competency questionnaires. The pre-course mean score was 64% and the post-course mean was 77.3% ($p<0.001$). The majority of participants reported to be highly satisfied with the course. They found it extremely useful (100%), and the learning activities were found to helpful (100%) and creative (95%). The questionnaire item *I would recommend online learning as a way to learn about infection control* was agreed upon by 100% of the respondents. Some dissatisfaction arose from receiving insufficient feedback at exercises, no opportunity to ask a question, the course taking longer than expected, and the hospital firewall making uploading slow or impossible.

The open-ended questionnaire items asking participants in what ways the course had been useful to them identified three major themes: improvement of hand hygiene practices; improvement of the teaching participants gave to patients, visitors and staff about how to use personal protective equipment; and improvement of their own techniques.

The authors conclude that interactive online learning can be a convenient and acceptable way for nurses to learn in the workplace. Moreover, they state that online learning can be considered an effective way to enhance knowledge and skills related to infection control and prevention.[394, 395]

Also in Canada, Bryce and colleagues[397] developed an e-learning module to deliver standardized infection control training to all healthcare professionals across a Canadian health authority. The course was developed by a multi-disciplinary team from a variety of health settings. Their objectives were reported to be to: (a) create a module that was relevant to day-to-day practice, accessible, clearly understood, consistent, and effective in transferring knowledge; (b) achieve acceptance and regular use of the course; and (c) demonstrate that the course transferred knowledge effectively. The course was interactive and included a variety of features such as drop and drag technology, animation and video. The learning objectives were fourfold: (1) awareness of the importance of infection; (2) familiarity with and application of routine infection control precautions in daily practice; (3) knowledge of how and when to use personal protective barriers; and (4) ability to describe the various types of isolation.

The outcomes identified as indicators of success of the online learning project were also fourfold: (1) obtain and demonstrate acceptance by key facility stakeholders; (2) assess, evaluate and document improvement in infection control knowledge after course completion; (3) document user satisfaction post-course; and (4) increase the number of clinicians that are taught the basic principles of infection control.

The authors state that the development of the module showed to be instructive for both the students and the infection control/education team, yielding an enhancement of knowledge regarding delivery of healthcare education using Web-based technology. Throughout the implementation process, insights were gained into combining valuable content with product user friendliness, and the importance of engaging key stakeholders in the development process. User feedback revealed that quiz questions were to be carefully constructed in order to precisely reflect course content and participant learning. The course was concluded to make learning of infection prevention and control more efficient, economical, effective, and pleasant. According to the authors, it succeeded in overcoming geographic barriers, time constraints and varying professional needs. Due to the extensive positive response, use of the module has been extended since to various health facilities in the region.[397]

3. The EVIDENCE Crash Course

Based on the article: Labeau S, Rello J, Dimopoulos G, Dicle A, Oztürk C, Vandijck D, Vandewoude K, Lipman J, Vogelaers D, Blot S, the EVIDENCE group. The value of E-learning for the prevention of healthcare-associated infections. Submitted.

Introduction

Healthcare-associated infections (HAIs) remain a major health threat as they affect 5% to 10% of patients in acute care hospitals, and up to 33% of those admitted to the intensive care unit (ICU).[1] The dreaded *Big Four* infection types accounting for more than 80% of all HAIs are ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), surgical site infection (SSI) and catheter-related urinary tract infection (CAUTI).[48] The impact of these adverse events in terms of excess morbidity and excess expenditures from both hospital and societal perspectives is highly detrimental.[398] The staggering gravity of the problem has led to a transition from accepting HAIs as an inevitable outcome of hospital admission toward a goal of zero tolerance.[1]

Fortunately, many HAIs are preventable. Up to 65%–70% of cases of CLABSI and CAUTI and 55% of cases of VAP and SSI are esteemed to be avoidable if current evidence-based strategies are applied.[7] Striving to raise awareness of these strategies among clinicians, authoritative organisations have bundled them into comprehensive evidence-based guidelines, which they made widely available and easily accessible.[3, 15]

Unsolicited distribution of guidelines as such has however been proven not to change clinicians practice.[21] Rello and colleagues investigated physicians' adherence to evidence-based guidelines for the prevention of VAP and found an overall self-reported non-adherence rate of 37%.[34] Ricart and colleagues repeated the same research in a sample of ICU nurses and found the non-adherence rate to be 22%.[23] Given the fact that self-reports are known to suffer from social desirability bias, the actual rates might even be higher than those reported. Besides a lack of compliance, extensive gaps in knowledge about guideline contents have been reported.[295-297, 333] Multiple choice knowledge tests about HAI prevention guidelines completed by a sample of over 3000 European ICU nurses yielded disappointing overall scores below the conventional 50% threshold to pass a test.[296, 297]

There is good evidence that effective educational interventions help to facilitate guideline implementation.[399] A shift of emphasis in education has been witnessed in the mid-nineties of the previous century from providing instruction to producing learning.[361] Critical thinking, independent and evidence-based learning, and feedback are since being regarded as indispensable features of this new learning paradigm.[362] Quite simultaneously, a rise in the use of information technologies in (medical) education took a start. E-learning, defined as a method which integrates information technology and the learning process by using material delivered through the internet,[363] was soon acknowledged to be a valuable educational tool.[364]

Today, a plethora of e-learning modules are available. A recent review of Web-based educational resources yielded a list of over 135 tools specifically developed for ICU clinicians.[390] Of these, none however focuses on the essentials of preventing HAI. We developed a Web-based crash course, bundling the essentials of evidence-based HAI prevention. This paper reports on the development of the EVIDENCE Crash Course and focuses on its contribution to the acquisition and retention of knowledge of evidence-based strategies for infection prevention.

Methods

Course development

The EVIDENCE Crash Course was developed in Dutch language using open source software eXe (http://exelearning.org) release 1.04.0.3532. Subsequently its lay-out was embellished by a web-designer. To- and back-translations of the course were effectuated in English, Portuguese, Spanish and Turkish languages. To optimise accessibility, a computer with internet access and a web browser are all that are needed to study the course; no plug-ins, additional software nor downloads are required.

Content validity was assessed and approved by an international team of experts in infection prevention (SB, DMV, JL, GD, JR). A sample of 50 potential users agreed upon its face validity and usability by means of the Software Usability Measurement Inventory® (SUMI®), a proven method of measuring software quality from the end user's point of view.[400]

Course contents

The EVIDENCE course consists of seven chapters. As the focus is on evidence-based practice, the first chapter is dedicated to this concept. The second chapter introduces the problem of HAIs and stresses on the importance of their prevention. As hand hygiene is key to preventing infection, this topic is discussed in the third chapter. Chapters four to seven, finally, focus on each of the *Big Four*, respectively. Each chapter can be studied separately with icons indicating which information is to be memorised or merely informative. Different types of exercises with immediate feedback, such as case studies, cloze exercises and multiple choice tests, are integrated to allow self-evaluation during the learning progress.

Depending on the participants' level of pre-knowledge, it was estimated that it would take three to five hours to master the course.

Recruitment of the sample

An international sample of voluntary learners was recruited through repeated international promotional campaigns. These included blast e-mails to all members of the Flemish Society for Intensive Care Nurses and the European Society for Intensive Care Medicine (ESICM) by whom the study was endorsed, distribution of e-flyers to professional organisations and members of existing networks, spreading flyers at (inter)national congresses.

As an incentive, a certificate of participation was acquired upon completion of the entire study path. The certificate was issued by European Society of Intensive Care Medicine (ESICM) who endorsed the EVIDENCE-project.

Inclusion and exclusion criteria

The course was originally designed for ICU clinicians. However, with the exception of VAP prevention, all topics included in the course are valid for non-ICU clinicians as well. In addition, numerous healthcare professionals working outside the ICU environment also explicitly showed interest. Therefore, involvement in in-patient care was set as the only inclusion criterion for study participation; no exclusion criteria were defined. As such, enrollment was open to all healthcare workers and students.

Enrollment

The study website www.evidenceproject.org was created to provide information about the study design, allow participants to grant informed consent, enroll and access the course. The

site also provided information on the background, aims and design of the study. The site was open for registration from 30 October 2010 till 31 December 2011.

Study path

Registered participants were guided through the study path by an automated e-mailing system: (a) a first e-mail invited them to log in to the study site and to complete a 50-item multiple choice knowledge test (Table 18) in order to measure baseline knowledge; (b) after electronic submission of this pre-test, access to the course was automatically granted for a maximal period of eight weeks. This period could, however, be ended earlier by the student whenever he felt mastering the course. After six weeks, students were alerted by automated e-mail about the imminent end of the study period; (c) access to the course was denied automatically after an eight weeks study period or as soon as the student himself indicated to be ready. Simultaneously, an automated e-mail was sent with the invitation to take a second 50-item multiple choice test. The questions of this test were identical to these of the pre-test, albeit differently ranked. This first post-test aimed to evaluate increase in knowledge immediately after studying the course; (d) twelve weeks after submission of the post-test, participants were invited by automated e-mail to complete a third and last 50-item multiple choice test. Again, its questions were identical to these of the previous tests, but differently ranked. This second post-test aimed to evaluate the extent of decrease in knowledge as compared to the first post-test, and to determine the residual knowledge by comparing its results with the results of the pre-test.

The multiple knowledge tests used had undergone face and expert content validation, and their reliability had been assessed using item analysis. Test scores were calculated as: correct answer = 1 point; wrong answer or 'I do not know' = 0 points. There was no correction for guessing.

Participants' actual study time was logged; time-outs with a need to re-log in occurred following five minutes of computer inactivity and with a warning popping up on the screen whenever such a time-out was near.

All transactions on the study site were closed as of 15 July 2012.

The study flow is represented in Figure 7.

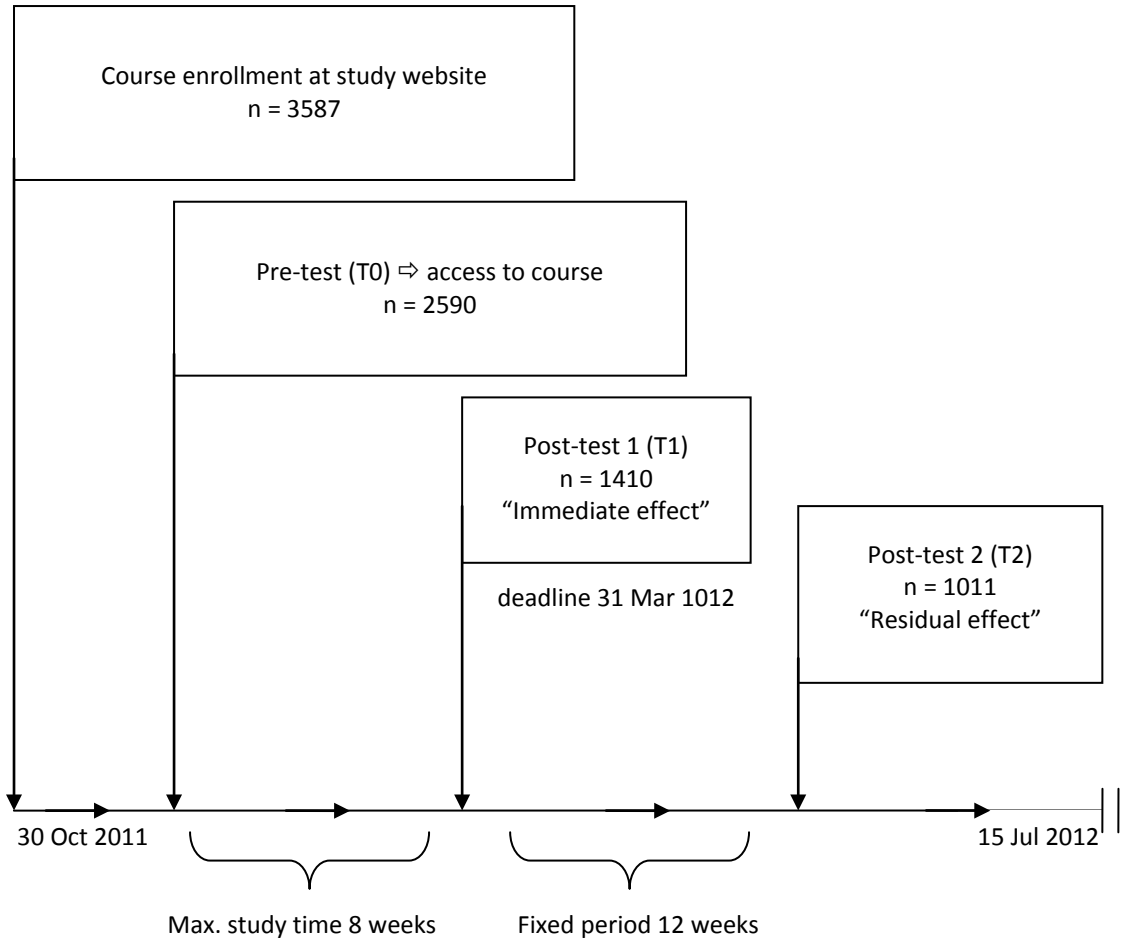

Figure 7: Study flow

Drop-out analysis

Following the end of the study, a one-question survey was e-mailed to all participants who had not completed the entire study path to identify their reasons for opting out.

Statistical analysis

Statistical analysis was performed using IBM SPSS for Windows 20·0 (IBM Corp., NY, US). Tests were two-tailed and statistical significance was set at $p<0{\cdot}05$. Not-normally distributed continuous variables are described as median (interquartile range; IQR). Univariate analysis was performed using Mann-Whitney U test, Wilcoxon Signed Ranks test or Kruskal-Wallis test as appropriate.

Table 18: Multiple choice knowledge test with correct answers underlined

1. **When a bedridden patient with an indwelling urinary catheter needs to be transported, the collector bag should be …**
   a. placed in the bed to avoid traction.
   b. hung beneath the bladder level to avoid reflux.
   c. clamped in order to avoid reflux.
   d. I do not know.
2. **When neither lipid emulsions, nor blood products are administered through a central venous catheter, it is recommended to replace the administration set ...**
   a. every 24 hours.
   b. every 48 hours.
   c. every 96 hours.
   d. I do not know.
3. **Concerning the use of gloves, which of the following statements is correct?**
   a. Gloves must be changed in between separated tasks on one patient when going from a dirty/contaminated to a clean body site.
   b. Gloves must be changed in between separated tasks on one patient when going from a clean to a dirty/contaminated body site.
   c. Gloves must not be changed in between separated tasks on one patient.
   d. I do not know.
4. **Following the available evidence on the prevention of surgical site infection, the appropriate time to shower or bathe with an uncovered incision is …**
   a. ≥ 48 hours following surgery.
   b. ≥ 96 hours following surgery.
   c. unresolved by lack of evidence.
   d. I do not know.
5. **Concerning the frequency of ventilator circuits changes in the prevention of ventilator-associated pneumonia …**
   a. it is recommended to change circuits every 48 hours (or when clinically indicated).
   b. it is recommended to change circuits every week (or when clinically indicated).
   c. it is recommended to change circuits for every new patient (or when clinically indicated).
   d. I do not know.
6. **It is recommended to replace central venous catheters routinely.**
   a. Yes it is, every seven days.
   b. Yes it is, every three weeks.
   c. No it is not, only when indicated.
   d. I do not know.
7. **Adequate handwashing with water and non-medicated soap should take …**
   a. one minute.
   b. 35 seconds.
   c. 20 seconds.
   d. I do not know.
8. **When using a chlorhexidine gluconate impregnated sponge instead of a standard dressing to cover up the insertion site of a central venous catheter, the risk of infection is …**
   a. reduced.
   b. increased.
   c. identical.
   d. I do not know.
9. **In settings with a high rate of catheter-related infection it is recommended to use a central venous catheter coated or impregnated with an antiseptic agent.**
   a. Yes it is, in patients whose catheter is expected to remain in place for more than five days.
   b. No it is not, because the use of such catheters is not cost-effective.
   c. No it is not, because the use of such catheters does not result in a significant decrease in the rate of catheter-related infections.
   d. I do not know.
10. **The need for continuing use of an indwelling urinary catheter must be assessed …**
    a. daily.
    b. every 48 hours.
    c. every 96 hours.
    d. I do not know.
11. **Elective surgery on patients with remote site infections should be postponed until the infection has resolved.**
    a. This is true for all patients.
    b. This is only true for debilitated patients.
    c. This is only true for patients infected with multi-resistant micro-organisms.
    d. I do not know.
12. **Concerning the use of open versus closed suction systems …**
    a. open suction systems are recommended.
    b. closed suction systems are recommended.
    c. both systems can be recommended.
    d. I do not know.
13. **To prevent central venous catheter-related infection, replacing central venous catheters over a guidewire is recommended.**
    a. Yes it is, every three days.
    b. Yes it is, every seven days.
    c. No it is not, only when indicated.
    d. I do not know.

14. Hospitalized patients at risk for healthcare-associated infections are ...
a. only those who are immunocompromized.
b. all patients, there are no prerequisite conditions.
c. only critically ill patients at the intensive care unit.
d. I do not know.

15. To prevent central venous catheter-related infection, it is recommended to cover up the catheter insertion site with ...
a. polyurethane dressing (transparent, semipermeable).
b. gauze dressing.
c. both are recommended because the type of dressing does not affect the risk of catheter-related infections.
d. I do not know.

16. In urinary catheterization, short-term catheterization is usually defined as catheter in place for less than …
a. three days.
b. seven days.
c. ten days.
d. I do not know.

17. When performing endotracheal suctioning …
a. it is recommended to wear non-sterile gloves.
b. it is recommended to wear sterile gloves.
c. it is not recommended to wear gloves.
d. I do not know.

18. In order to prevent ventilator-associated pneumonia, it is recommended to elevate the head of the bed in mechanically ventilated patients to …
a. 5° to 15°.
b. 30° to 45°.
c. 50° to 60°.
d. I do not know.

19. In between fluffing up the pillows on the beds of two different patients, it is recommended to perform …
a. handwashing with water and non-medicated soap only, no need to disinfect with alcoholic hand rub.
b. handwashing with water and non-medicated soap, followed by hand antisepsis with alcoholic hand rub.
c. hand antisepsis with alcoholic hand rub only.
d. I do not know.

20. To prevent central venous catheter-related infection, it is recommended to replace pressure transducers and tubing routinely.
a. Yes it is, every four days.
b. Yes it is, every eight days.
c. No it is not, only when indicated.
d. I do not know.

21. To prevent surgical site infection, it is recommended to protect a primarily closed incision …
a. during the first 12 hours following surgery.
b. during the first 24-48 hours following surgery.
c. during the first 5 days following surgery.
d. I do not know.

22. Surveillance succeeds in reducing the incidence of surgical site infection.
a. Yes it does, and without supplementary preventive measures.
b. Yes it does, but only when accompanied by supplementary preventive measures.
c. No it does not, surveillance only helps to gain insight into the prevalence of infection, but has no influence on incidence rates.
d. I do not know.

23. In the prevention of healthcare-associated infection, so-called 'Standard precautions' apply to ...
a. all healthcare professionals in all healthcare settings when caring for infected patients.
b. all healthcare professionals in all healthcare settings when caring for colonized patients.
c. all healthcare professionals in all healthcare settings when caring for all patients.
d. I do not know.

24. If in the pre-operative period a surgical patient's hair at or around the incision site interferes with the operation, it is recommended to remove it by …
a. razor shave.
b. depilatory agents.
c. electric clippers.
d. I do not know.

25. Concerning oral versus nasal endotracheal intubation in the prevention of ventilator-associated pneumonia …
a. oral intubation is recommended.
b. nasal intubation is recommended.
c. both routes of intubation can be recommended as the route of endotracheal intubation does not affect the risk of VAP.
d. I do not know.

26. When wearing non-sterile gloves during direct patient care, contamination of the skin on the healthcare worker's hands …
a. is not possible.
b. is possible, regardless the profile of the patient cared for.
c. is possible, but only in case of contact with an infected patient.
d. I do not know.

27. **When using closed systems for endotracheal suctioning, which of the following statements is correct when aiming to prevent ventilator-associated pneumonia?**
    a. Daily changes are recommended (or when clinically indicated).
    b. Weekly changes are recommended (or when clinically indicated).
    c. It is recommended to change systems for every new patient (or when clinically indicated).
    d. I do not know.
28. **When emptying the drainage bag of a patient with a urinary catheter, …**
    a. it is recommended to wear non-sterile gloves.
    b. it is redommended to wear sterile gloves.
    c. it is not redommended to wear any gloves.
    d. I do not know.
29. **When aiming to prevent ventilator-associated pneumonia, which of the following statements concerning endotracheal tubes with an extra lumen for suctioning subglottic secretions is correct?**
    a. These tubes reduce the risk of ventilator-associated pneumonia.
    b. These tubes increase the risk of ventilator-associated pneumonia.
    c. These tubes do not influence the risk of ventilator-associated pneumonia.
    d. I do not know.
30. **After moving a family picture on the bedside table of the patient, it is recommended to perform …**
    a. handwashing with water and non-medicated soap only, no need to disinfect with alcoholic hand rub.
    b. handwashing with water and non-medicated soap, followed by hand antisepsis with alcoholic hand rub.
    c. hand antisepsis with alcoholic hand rub only.
    d. I do not know.
31. **In patients with an indwelling urinary catheter, it is recommended to …**
    a. disinfect the meatus with an antiseptic solution.
    b. perform routine meatal hygiene only.
    c. disinfect the meatus with an antiseptic solution followed by application of an antibiotic ointment.
    d. I do not know.
32. **To prevent central venous catheter-related infection, it is recommended to change the dressing on the catheter insertion site ...**
    a. on a daily basis.
    b. every three days.
    c. when indicated (soiled, loosened, ...) and at least weekly.
    d. I do not know.
33. **After bathing a patient infected with methicillin-resistant *Staphylococcus aureus*, healthcare workers with non-visibly soiled hands should perform …**
    a. handwashing with water and non-medicated soap only, no need to disinfect with alcoholic hand rub.
    b. handwashing with water and non-medicated soap, followed by hand antisepsis with alcoholic hand rub.
    c. hand antisepsis with alcoholic hand rub only.
    d. I do not know.
34. **When lipid emulsions are administered through a central venous catheter, it is recommended to replace the administration set ...**
    a. within 24 hours.
    b. every 72 hours.
    c. every 96 hours.
    d. I do not know.
35. **The prevalence of healthcare-associated infection in developed countries is about ...**
    a. 1% to 5%.
    b. 5% to 15%.
    c. 15% to 20%.
    d. I do not know.
36. **Hospital-acquired infection is a synonym of …**
    a. healthcare-associated infection.
    b. nosocomial infection.
    c. community-acquired infection.
    d. I do not know.
37. **The most important risk factor identified in the development of catheter-associated urinary tract infection is …**
    a. colonization of the drainage bag.
    b. diabetes mellitus.
    c. duration of catheterization.
    d. I do not know.
38. **To prevent central venous catheter-related infection, it is recommended to disinfect the catheter insertion site with an antiseptic containing ...**
    a. 2% chlorhexidine.
    b. 0,5 % chlorhexidine.
    c. 10% povidone-iodine.
    d. I do not know
39. **Ventilator-associated pneumonia is defined as pneumonia that develops more than … to … hours after intubation and initiation of mechanical ventilation.**
    a. 24 to 48.
    b. 48 to 72.
    c. 72 to 96.
    d. I do not know.

40. The term 'primary bloodstream infection' refers to …
   a. a bloodstream infection in which there is no obvious source of infection.
   b. a bloodstream infection in which there is an obvious source of infection.
   c. the first episode of a bloodstream infection.
   d. I do not know.

41. In urinary catheterization, long-term catheterization is usually defined as catheter in place for more than …
   a. 15 days.
   b. 20 days.
   c. 28 days.
   d. I do not know.

42. In the pathogenesis of ventilator-associated pneumonia, the most significant treatment-related factor contributing to impaired host defences is …
   a. the use of a ventilator.
   b. the use of an endotracheal tube.
   c. the use of a nasogastric tube.
   d. I do not know.

43. The pathogens that cause surgical site infection are usually microorganisms that originate from …
   a. the patient's endogenous flora.
   b. contaminated equipment.
   c. the hands of healthcare workers.
   d. I do not know.

44. In patients with an indwelling urinary catheter, urinary tract infection is usually …
   a. non-existing.
   b. asymptomatic.
   c. easily clinically detectable.
   d. I do not know.

45. In intubated and mechanically ventilated patients, it is recommended to maintain the pressure of the endotracheal tube cuff between …
   a. 10 – 20 cmH_2O.
   b. 20 – 30 cmH_2O.
   c. 30 – 40 cmH_2O.
   d. I do not know.

46. After bathing a patient infected with *Clostridium difficile*, healthcare workers' non-visibly soiled hands should be …
   a. washed with water and non-medicated soap only, no need to disinfect with alcoholic hand rub.
   b. washed with water and non-medicated soap, then disinfected with alcoholic hand rub.
   c. disinfected with alcoholic hand rub only.
   d. I do not know.

47. Nosocomial pneumonia is defined as …
   a. pneumonia occurring 48 hours or less after hospital admission
   b. pneumonia occurring 48 hours or more after hospital admission
   c. pneumonia occurring at any time after hospital admission
   d. I do not know

48. When comparing hand hygiene using alcohol-based hand rubs with handwashing using water and non-medicated soap …
   a. hand hygiene using alcohol-based hand rubs requires less time than handwashing with water and non-medicated soap.
   b. hand hygiene using alcohol-based hand rubs requires more time than handwashing with water and non-medicated soap.
   c. hand hygiene using alcohol-based hand rubs and handwashing with water and non-medicated soap require an equal amount of time.
   d. I do not know.

49. Which of the following precautions is part of the universal transmission-based precautions?
   a. contact precautions.
   b. isolation precautions.
   c. colonization precautions.
   d. I do not know.

50. During insertion of an indwelling urinary catheter, extraluminal contamination occurs …
   a. by the hands of healthcare professionals.
   b. by microorganisms ascending from the perineum or the urethral meatus.
   c. by microorganisms descending from the bladder.
   d. I do not know.

To evaluate the course's effect in relation to learners' countries' human development level, the Education and Health ranking from the 2011 Education and Health Human Development Report of the United Nations Development Program was used, which categorises countries into very high, high, medium or low human development.[401]

The immediate learning effect was calculated by subtracting the median score (%) at T1 from the median score at T0, and the residual learning effect by subtracting the median score at T2 from T0. The difference between the median test scores at T1 and T2 indicated the decrease in knowledge after 3 months without accessing the course. Learning effects are reported as percentages (either positive or negative) with corresponding interquartile ranges (IQR). All variables with p<0·05 in univariate analysis were included in a multivariate linear regression analysis using the Enter-method, and assessed for multicollinearity. A stepwise elimination of variables with p>0·20 was predefined to develop the final model.

Ethical considerations

Upon enrollment, potential participants were required to give informed consent by ticking a box in the electronic registration form in order to start the study. The study was reviewed and approved by the ethics committee at Ghent University Hospital (registration codes B67020072039 and B67020108358).

Results

Description of the sample

3587 healthcare workers representing 79 nationalities enrolled in the course. Of these, 2590 (72·2%) submitted the pre-test, 1410 (39·8%) actually studied the course and submitted post-test 1, and 1011 (28·2%) also submitted post-test 2, thus completing the entire study path.

Of the actual learners (n=1410), 1184 (84·0%) were female; most students had >10 years of working experience (n=699; 49·6%), worked in a mixed ICU (n=495; 35·1%), and in a university hospital (n=685; 48·58%); 1046 (74·18%) were nurses, 125 (8·86%) were physicians, 60 (4·25%) students, and 179 (12·69%) were other healthcare professionals. Their median age was 33 years (IQR 28–40). The median study time was 194 minutes (IQR 96–306). For further categorisation, study time quartiles were defined conveniently as <100 minutes (median 45; IQR 24–70; n=371), 100–200 minutes (156; IQR 127–178; n=353), 201–300 minutes (243; IQR 223–269; n=318), and >300 minutes (405; IQR 344–502; n=368).

Test scores and learning effects

The median score on the pre-test was 52% (IQR 44–62; n=2590), increasing to 80% (IQR 68–88) at post-test 1 (n=1410) and amounted to 74% (IQR 64–84) on post-test 2 (n=1011). The

overall immediate learning effect, defined as the difference in scores between the pre-test and post-test 1, was 24% (IQR 12–34; p<0.001; n=1410), decreasing with -6% (18%; IQR -12–2; p<0.001; n=1011) after 3 months (difference in scores between post-test 1 and post-test 2; n=1011). The overall residual effect, i.e. the difference in scores between the pre-test and post-test 2, remained 18% (IQR 8–28; p<0.001; n=1011).

For all course topics, positive immediate and residual learning effects were found (Table 19). Gains in knowledge increased with study time. The immediate effect reached a maximum as from 200 study minutes (28%) while the residual effect was greater once study time exceeded 300 minutes (Table 20).

Table 20 shows the median immediate and residual effects according to the learners' characteristics, and the median decrease in knowledge after a 3 months period without accessing the course.

Variables for which statistically significant differences between groups were found in univariate analysis were entered in a multivariate linear regression model (Table 21). For the immediate learning effect, an increase in age category showed to be independently associated with a smaller learning effect, and a longer study time was found to be associated with a better immediate learning effect (R^2=0·18). Being female, longer study time and working in a non-ICU-related environment were found to predict better residual learning effects (R^2=0·32). Multicollinearity analysis detected no correlations between the variables entered.

Drop-out analysis

The survey inquiring about learners' reasons to end participation obtained 503 responses. A lack of time was identified as the main reason (n=211; 42%) for opting out. Further, learners indicated having forgotten their enrollment (n=146; 29%) and problems with computer / internet connection (n=52; 10%) as the main reasons for not completing the study path.

Table 19: Median scores and learning effect of the total course (overall) and per category of questions

	pre-test n = 2590	**post-test 1 n = 1410**	**Immediate effect Δ pre-test – post-test 1 n = 1410**	**post-test 2 n = 1011**	**Decrease in knowledge after 3 months Δ post-test 1 – post-test 2 n = 1011**	**Residual effect Δ pre-test – post-test 2 n = 1011**
Overall (total course) **(n = 50)**	52 (44–62)	80 (68–88)	24 (12–34)	74 (64–84)	-6 (-12–2)	18 (8–28)
Urinary Tract Infection (n = 8)	50 (38–63)	88 (63–100)	25 (13–38)	75 (63–88)	0 (-25–0)	13 (0–38)
Central Venous Catheter-related Infection (n = 11)	45 (36–67)	82 (64–91)	27 (9–36)	73 (55–91)	-9 (-18–0)	18 (0-36)
Ventilator-Associated Pneumonia (n = 10)	50 (40–70)	80 (70–90)	20 (10–40)	80 (70–90)	0 (-10–0)	20 (0–30)
Surgical Site Infection (n = 6)	33 (17–50)	84 (50–100)	33 (17–-67)	67 (50–83)	-17 (-33–0)	17 (0–50)
Hand Hygiene (n = 10)	60 (50–70)	70 (60–80)	10 (0–20)	70 (60–80)	0 (-10–10)	10 (0–20)
Theoretically oriented questions (n = 7)	43 (29–57)	71 (57–86)	29 (14–43)	71 (57–86)	0 (-14–0)	14 (0–43)
Practically oriented questions (n = 43)	53 (47–63)	81 (70–88)	21 (12–33)	77 (65–86)	-5 (-12–0)	16 (7–28)

Data are reported as % (interquartile range)

Δ pre-test – post-test 1: immediate learning effect; Δ post-test 1 – post-test 2: mid-long-term learning effect; Δ pre-test – post-test 2: residual learning effect

IQR: interquartile range; n in rows: number of questions; n in columns: number of learners

Table 20: Learning effects according to learners' characteristics

	Immediate effect Δ pre-test – post-test 1 n = 1410		p	Decrease in knowledge Δ post-test 1 – post-test 2 n = 1011		p	Residual effect Δ pre-test – post-test 2 n = 1011		p
	% (IQR)	n		% (IQR)	n		% (IQR)	n	
Sex									
male	22 (10–32)	226	0·143	-8 (-16–(-2))	168	<0·001*	12 (4–20)	168	<0·001*
female	24 (12–34)	1184		-4 (-12–2)	843		20 (8–30)	843	
Age									
<29 years	24 (8–35)	442	0·018*	-6 (-14–0)	275	0·290	20 (8–30)	275	0·003
29–34 years	25 (12–34)	364		-6 (-12–2)	273		20 (10–32)	273	
35–41 years	22 (14–32)	306		-6 (-12–0)	232		15 (6–26)	232	
>41 years	20 (10–32)	198		-4 (-12–2)	231		16 (6–26)	231	
Work experience									
<1 year	22 (6–36)	103	0·185	-8 (-14–0)	55	0·039*	18 (6–28)	55	0·797
1–5 years	26 (10–36)	321		-8 (-14–0)	214		20 (8–30)	214	
6–10 years	24 (12–32)	287		-4 (-12–2)	203		18 (8–28)	203	
>10 years	22 (12–32)	699		-4 (-12–2)	539		18 (8–28)	539	
Profession									
Nurse	24 (12–34)	1046	0·096	-6 (-12–2)	739	0·001*	18 (8–28)	739	0·144
Physician	24 (12–32)	125		-10 (-16–(-4))	86		14 (8–20)	86	
Student	30 (11–42)	60		-8 (-16–2)	40		18 (6–30)	40	
Other	22 (12–30)	179		-4 (-10–2)	146		17 (8–28)	146	
Work environment									
ICU and ICU-related	22 (12–32)	878	0·019*	-6 (-14–0)	628	0·032*	16 (6–26)	628	<0·001*
non-ICU-related	24 (12–34)	532		-4 (-10–2)	383		20 (8–32)	383	
Study time									
<100 min.	10 (2–22)	371	<0·001*	-2 (-8–4)	191	<0·001*	10 (2–24)	191	<0·001*
100–200 min.	22 (14–32)	353		-8 (-14–0)	276		14 (6–24)	276	
201–300 min.	28 (18–36)	318		-8 (-14–(-2))	241		18 (8–28)	241	
>300 min.	28 (20–36)	368		-4 (-10–2)	303		24 (16–34)	303	
Education & health index									
Low and medium HD	22 (6–33)	74	0·466	-6 (-12–0)	51	<0·001*	16 (6–26)	51	<0·001*
High HD	24 (12–34)	809		-4 (-10–3)	562		20 (8–32)	562	
Very high HD	22 (12–32)	527		-6 (-14–(-2))	398		14 (6–26)	398	

Δ: increase / decrease in test scores (%) reported as median (interquartile range)
Study time and age: intervals based on quartiles
n: number of participants; ICU: intensive care unit; HD: human development; *statistical significance

Table 21: Multivariate linear regression analysis

Immediate learning effect			
	B ± standard error	**95% confidence interval**	**p**
Age (per class increase) *	-1·8% ± 0·3	-2·4–(-1·1)	<0.001
Study time (per class increase) †	5·6% ± 0·3	4·9–6·2	<0.001
R^2: 0·176			
Residual learning effect			
	B ± standard error	**95% confidence interval**	**p**
Female gender	4·3% ± 1·3	1·8–6·9	0·001
Non-ICU related work environment	2·3% ± 1·0	0·3–4·3	0·026
Study time (per class increase) †	4·0% ± 0·4	3·1–4·8	<0·001
R^2: 0·325			

*** <29 years, 30–34 years, 35–41 years, or >41 years of age**
† <100 min., 101–200 min., 201–300 min., or >300 min. study time

Discussion

The present study found that limited time invested in studying a Web-based course on the essentials of HAI prevention with good usability and exercises for self-evaluation yielded significant increases in immediate (+24%) and residual (+18%) learning effects among nurses, physicians and students. Although the course was originally developed for ICU clinicians, healthcare professionals working outside the ICU also showed significant benefit from studying the course.

A 2009 systematic review of 130 articles published between 1990 and 2007 reported comparisons of internet-based instructional methods against no intervention, of which 126 evaluated knowledge outcomes.[402] The pooled effect size for these studies was 1·0, meaning that, overall, e-learning improved knowledge by one standard deviation. The standard deviation found in the review being 12% consequently suggests that an average improvement of test scores by about 12% can be expected from an e-learning intervention.[402]

Our study resulted in an overall immediate learning effect of 24%, thereby doubling the expected improvement. The effect decreased to 18% after three months without accessing the course, thereby still yielding an enhancement in knowledge that equals 150% of the expectations. However, as studying our course was voluntary, selection bias needs to be taken into account when interpreting our results. Presumably, participants who enrolled were motivated and interested in the topic. In turn, the most motivated and most interested among them might have completed the entire study path, thus generating better learning

effects than if participation had been obligatory among a random sample. On the other hand, this may also imply that the pre-knowledge level of our participants was higher as compared to the general population of healthcare workers. If so, the learning effects in a random sample of clinicians might exceed these identified in the current study. Selection bias is nevertheless, at least partially, corrected for by the fact that during the study course numerous clinicians indicated to participate in order to obtain the certificate of participation issued by the ESICM. This motive for participation might partly alleviate the bias caused by voluntary enrollment.

Education of all members of the multidisciplinary team is considered a first and crucial requirement when targeting implementation of interventions for infection prevention.[74] Thought should however be given to the fact that clinicians may find it problematic to attend conventional educational sessions. They often work irregular shifts, may have assignments in different hospitals or find it hard to prioritise attending sessions in times of restricted staffing. E-learning offers a solution as it allows healthcare workers to study where and when they prefer to, and at their own pace.[364] Besides, e-learning has additional important assets as it combines important learning principles such as student activity, individual learning, rapid response, and repetition according to requirements. It promotes independent skills, allows flexible working and encourages the development of skills in time management, organisation, and self-pacing.[363] Finally, it provides an opportunity for practising computer skills, and encompasses a pedagogical approach that typically aspires to be flexible, engaging and learner-centred.[363, 372, 374, 375]

Using e-learning for staff education can also be advantageous for the healthcare setting. Institutions may provide tailor-made educational packages in order to meet employees specific learning objectives.[403] If desired, e-learning allows to log participants' actual course attendance, study time, test scores and study progress. Costs associated with the development of e-modules will predominantly depend on the software used and the investment in personnel cost. Developed by the researcher (SL) using open source software, the development costs for the EVIDENCE course were very limited. In environments or economic climates where restricted resources for educational purposes are to result in both efficient and effective learning, the use of open source software could prove to be highly advantageous. In addition, as e-learning allows repetition of study activities at institution- or

ward-tailored basis, the concept may contribute to an increase in general awareness about the problem of HAIs and as such, to a positive change in attitudes towards the problem.

The drop-out rate from our course was high. Of all clinicians enrolled, only 40% actually studied the course (1410/3587). Isolation of learners has been identified as a common reason for high drop-out rates.[376] Our drop-out survey identified a lack of time as the main reason for opting out. As our sample merely consisted of voluntary students, a high drop-out rate is hardly unexpected as work, family life and personal commitments are easily prioritised.

Additional research comparing different Web-based interventions is needed to elucidate how to implement e-learning most effectively. In the meantime, our study strongly suggests that moderate time invested in a low-cost e-course with good usability features and exercises for self-evaluation can significantly enhance knowledge of HAI prevention. We therefore encourage institutional decision-makers to consider the use of e-learning in healthcare settings.

Conclusion of part three

In the past decades, e-learning has been acknowledged as a valuable tool for adult learning. Also education for healthcare workers has witnessed a shift from one devoid of significant computer-based resources to that where such tools are regularly incorporated.

Among its advantages, e-learning allows learners to study at the place and time best meeting their requirements, and at their own pace. Also for the health facility, multiple advantages are associated with the use of Web-based resources for education of staff.

In the field of e-learning for healthcare professionals, the considerable heterogeneity and small sample sizes in studies comparing e-learning with non-Web-based interventions hampers meta-analyses to draw clear-cut results. Internet-based resources incorporating features of interactivity, practice exercises, repetition, and feedback were however shown to be overall associated with improvements in learning outcomes.

Specifically for critical care providers, an extensive list of educational e-resources appears to be available. Among these, only four relate to the broad field of infectious diseases, covering specialised topics mainly for advanced learners. A number of local initiatives to develop and evaluate e-learning on the prevention and control of infection have been reported. Of these, none has specifically been focusing on the prevention of healthcare-associated infection.

A concise and comprehensible course focussing on the prevention of HAIs that is easily accessible and based on international evidence-based guidelines appeared to be missing from the list of e-courses available today for healthcare workers. By developing the EVIDENCE Crash Course, we attempted to fill this gap. An assessment of the course's effectiveness in increasing knowledge yielded positive findings, with overall significant learning effects that were sustained after three months without access to the course.

EPILOGUE

Throughout the EVIDENCE-project, knowledge of healthcare professionals was the common outcome of all studies conducted. The project started off with a needs analysis, investigating ICU nurses' knowledge about the prevention of VAP, CVC-RI and SSI, partially on a European scale. Regrettably, overall low knowledge levels were found, with test scores not reaching the conventional 50% threshold to pass a test.

The e-learning EVIDENCE *Crash Course* developed aimed to meet the needs detected by offering healthcare workers worldwide a comprehensive and comprehensible educational resource that would be readily available to study the essentials of evidence-based infection prevention whenever and wherever learners prefer, and at their own pace. Immediately after studying the course, knowledge levels demonstrated a significant increase which was substantially sustained after three months without access to the course.

There is no hard evidence available that allows for a direct linking of the low rates in adherence to evidence-based guidelines reported in the literature to low levels of knowledge about guidelines' contents. Nevertheless, it is merely logical to assume that compliance needs to be preceded by a thorough knowledge about the related recommendations. Thereby, knowledge is a *condition sine qua non* for compliance, a first and primordial requirement that needs to be fulfilled.

Healthcare workers will only be able to provide excellent patient care if they are well equipped with knowledge to underpin their daily care routines. Evidence-based guidelines for the prevention of HAI have acknowledged education of healthcare workers to be a first requirement that needs to precede the initiation of structured programs for infection prevention or overall quality improvement.[14, 15, 86, 88, 89, 92] One method proposed is to require healthcare personnel to complete an educational program including a posteducation test to ensure their knowledge and competency.[88] For such purposes, the use of e-courses could be of great benefit.

The value of increasing healthcare workers knowledge for the reduction of HAIs has largely been demonstrated by the results of educational programs worldwide.[38, 39, 41, 68, 72, 341] Also systematic reviews that synthesised the results of separate studies concluded in favour of adequate education and training of healthcare workers.

A 1995 systematic review of relevant data sources from 1975 to 1994 investigated the effectiveness of education strategies designed to change physician performance and health care outcomes.[105] Of 99 trials included (160 interventions) almost two thirds of the interventions (101/160) revealed an improvement in at least one major outcome measure: 70% demonstrated a change in physician performance, and 48% of interventions aimed at health care outcomes yielded a positive change.[105]

A more recent systematic review dated 2008[149] focussed on the field of infection prevention by determining the effect of educational strategies of healthcare providers on the reduction of HAI rates. Multiple computerised databases for the years 1966 to 2006 were searched, and supplemented by manual searches for relevant materials. A total of 26 studies using various educational programs for varied study populations of healthcare workers were included, most of them implemented in the ICU. Infection rates significantly decreased following the educational program in 21 studies, with risk ratios ranging from 0 to 0.79. The authors conclude that the implementation of educational interventions may reduce HAI rates considerably. They recommend to cluster randomized trials using validated educational interventions and costing methods to determine the independent effect of education on reducing HAI rates and the cost-savings that may accompany this approach.[149]

Our needs analysis on a European scale revealed that, overall, more experienced nurses had a better knowledge of prevention guidelines than their less experienced colleagues. Participants with less than one year working experience in the ICU yielded the lowest scores. A potential positive interpretation of this finding could be that the ICU is a stimulating work environment that encourages learning and promotes gathering of knowledge during the course of nurses' careers.

A more negative interpretation, however, could be that European institutes for nursing education do not succeed in satisfactorily preparing students to work in the complex ICU environment. Thereby, newly recruited nurses would struggle with a considerable lack of general knowledge when making their first steps in the job and would need at least a couple of years to catch up with their more experienced colleagues.

Throughout Europe, there is indeed an enormous variety in the duration, level and content of the courses leading to a specialised degree in ICU nursing, as well as in the nature and level of the institutions providing this education.[296, 404, 405] Although regrettable, this is not

surprising given the fact that in Europe even for the preregistration, basic nursing education programs a myriad of arrangements is still available.[406]

Back in 2004, the European federation of Critical Care Nursing associations (EfCCNa) launched a position statement on the post-registration ICU nursing education within Europe to overcome this issue and promote uniformity.[405, 407] To date, however, national and even local disparities still abound, while in today's globalising society the need for a pan-European high quality qualification for ICU nurses has only become more pressing. Therefore we plea for a pan-European curriculum for (post-registration ICU) nurses, in order to obtain equal educational requirements and thereby ensure high quality care across contemporary Europe.

Besides a pan-European curriculum, developing pan-European guidelines for infection prevention would help to rationalize conflicting recommendations. Based on the results of our needs analysis, it can be assumed that international recommendations may not always accord with countries' national or even local institutional guidelines. Although guidelines doubtlessly need to be tailored to institutions' specific cultural and organisational context, the evidence base of recommendations will remain unchanged. As a consequence, besides a lack of knowledge or deficiencies in training, the poor test scores obtained by European nurses in our studies may reflect differences in what is regarded as good practice, and/or a lack of consistent policy.

Throughout the EVIDENCE-project, the overall limitation of studies was the use of convenience samples. The related selection bias undeniably has to be taken into account when interpreting any of our results. The major strength of the project is the large numbers of participants in all studies conducted.

Also, the EVIDENCE-project revealed to contribute to the enhancement of nursing practice worldwide. In the course of years, we received various requests to use the questionnaires developed for the needs analysis in local research or quality improvement initiatives. Table 22 shows the list of countries from which requests were received to use the EVIDENCE questionnaires in local quality improvement initiatives. Besides, it is not improbable that similar initiatives have been taken in other countries as, once published, the questionnaires became available for all healthcare workers interested in their use.

Table 22: Known countries with quality improvement initiatives using the EVIDENCE questionnaires

Continent	Country
Europe	Austria
	Belgium
	Cyprus
	Denmark
	Finland
	Germany
	Ireland
	Italy
	Malta
	Netherlands
	Norway
	Scotland
	Spain
	Switzerland
Eurasia	Turkey
Asia	Indonesia
	Iran
	Japan
	Jordan
	Korea
	Malaysia
	Pakistan
	Palestine
	Philippines
	Taiwan
Africa	Botswana
	Egypt
	Kenya
	South-Africa
North America	Canada
	Mexico
	United States
	Arizona
	California
	Florida
	Illinois
	Kentucky
	Massachusetts
	New York
	Oklahoma
	Rhode Island
	South Carolina
	Virginia
	Wisconsin
South America	Argentina
Oceania	Australia

In conclusion, some recommendations can be made, based upon the outcomes of this thesis.

Institutions for nursing education, and for the healthcare professions in general, could be recommended to stress the importance of prevention of HAIs throughout their curricula. Today, the topic is often addressed in the basic module of the educational trajectories only, merely focussing on the main principles of hospital hygiene and microbiology. Given the poor knowledge levels as revealed by our knowledge tests, educational institutions should consider integrating repeated courses on the prevention of HAIs throughout the various modules of the curricula. These courses should be based on the latest evidence and discuss more detailed issues, such as site-specific infections. Preferably, education should not be restricted to traditional lectures but include activating and interactive learning methods, including cases, skills training, and simulation to optimise learning effects. Courses should be followed by regular and scheduled assessments in order to evaluate students' learning process and levels of knowledge.

Additionally, and as mentioned above, institutions for nursing and healthcare education throughout Europe should be encouraged to join in a more comprehensive debate about the implementation of transparent higher educational programmes which are comparable and compatible. The Sorbonne declaration of 25th of May 1998 emphasised the creation of the European area of higher education, and the objectives of the subsequent Bologna Declaration (19 June 1999) included the promotion of the necessary European dimensions in higher education, including curricular development and interinstitutional co-operation of study, training and research. With respect to education on infection prevention, standardized high quality education could help to enhance and equate knowledge levels among healthcare providers, which, in turn, might lead to pan-European improved practice.

If higher education must scale up with curricula that equip teachers to provide individuals with the knowledge and skills needed in the twenty-first century, educational approaches such as distance learning and e-learning are required. Therefore, it is recommended that educational institutions fully invest in training of staff to fulfil these functions in evolving teaching and learning systems.

The EVIDENCE course developed within this project, could prove a valuable instrument for both regular and distance learning students, and the knowledge tests could be used as reliable assessment tools. However, as all are based on evidence-based guidelines, they

require regular updating according to new evidence, whenever this becomes available. Modifications and updating need to be followed by new validation and reliability testing processes. Therefore, systematic reconsideration of these tools is necessary in order to maintain their value for educational purposes.

Education on the prevention of HAIs should not take a halt after healthcare professionals' graduation. Provision of evidence-based care in daily practice implies continuing and continuous efforts to remain aware of the latest recommendations. Healthcare facilities could therefore be recommended to systematically include topics on the prevention of infections in their programmes for employees' continuing education, for example by means of e-learning. Nurses, and healthcare professionals in general, should consider it a professional responsibility to keep themselves updated on the most recent, evidence-based information in order to ensure patient safety and provide high quality standards of care. An up-to-date e-learning course containing this information and provided by their employers could offer an excellent compromise between reducing the burden of individual and repeated searches for the latest information and taking responsibility for their personal professional development.

Recently, hospitals in Flanders started to strive, on a voluntary basis but strongly encouraged by Flemish governmental policy, towards accreditation. Accreditation is a process in which a third party provides a certificate of guarantee that a product, process or product meets specifically set standards of quality. In Flanders, hospitals aim to obtain accreditation through an organisation certified by the International Society for Quality in Healthcare (ISQua), i.e. the Joint Commission International (JCI) or the NIAZ (Nederlands Instituut voor Accreditatie in de Zorg). While in Flanders quality indicators are being established and validated today to guide the accreditation processes, the JCI has included documented HAI prevention strategies and training of staff as basic requirements for determining the quality standards of healthcare facilities.[408] As e-learning allows for objectively demonstrating and documenting of employee educational processes and outcomes, it may be recommended to include this learning method among training tools of hospitals striving to obtain accreditation.

Future research based upon the current results of the EVIDENCE-project could focus on determining outcomes in terms of infection rates in units or healthcare facilities where the

Crash Course is used as an educational tool. As various potential confounders could easily bias the results of such pre-postdesign study, a solid surveillance system and an extensive support on both the level of the unit and the organisation would be crucial prerequisites for all institutions participating in these proposed further evaluations. Cost-benefit analyses should accompany or follow investigations on clinical outcomes in order to determine and support most optimal implementation.

Due to restricted financial resources, the EVIDENCE course was developed with open source software and by the author of this thesis. Cooperation with industrial partners, various stakeholders and funding sources would allow to develop a more interactive instrument including video and sound, simulation, chat technology and online teacher-student communication tools. These activating learning methods could improve the course, and potentially reduce high drop-out rates caused by students feeling isolated when studying online. Moreover, it is important to stress that the current format of the EVIDENCE course does not allow for obtaining nor evaluating complex levels of knowledge about HAI prevention. The integration of cases and more complex, practice-guided and interactive learning materials might contribute to alleviate this limitation and is therefore recommended as an additional subject for further investigations. Also, and as mentioned above, future research focussing on the maintenance of the topical value, validity and reliability of the questionnaires and course developed within this project is required.

Healthcare-associated infections are a major, world-wide and timely societal problem. With the EVIDENCE project, we have aimed to enhance knowledge of healthcare professionals with respect to this issue. Although the project has various limitations, we hope to have contributed to raising awareness of the problem and, hopefully, to enhancing patient safety.

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ADDENDA

ADDENDUM 1: LIST OF ABBREVIATIONS

BSI	BloodStream Infection
CAUTI	Catheter-Associated Urinary Tract Infection
CDC	Centers for Disease Control and Prevention
CLABSI	Central Line-Associated BloodStream Infection
CR-BSI	Catheter-Related BloodStream Infection
CVC	Central Venous Catheter
CVC-RI	Central Venous Catheter-Related Infection
CVI	Content Validity Index
EfCCNa	European federation of Critical Care Nursing associations
EPIC II	Extended Prevalence of Infection in Intensive Care
ESICM	European Society for Intensive Care Medicine
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation System
HAI	Healthcare-associated infection
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IHI	Institute of Healthcare Improvement
IOM	Institute of Medicine
NHSN	National Healthcare Safety Network
SHEA	Society for Healthcare Epidemiology of America
SSI	Surgical Site Infection
UTI	Urinary Tract Infection
VAP	Ventilator-Associated Pneumonia

ADDENDUM 2: LIST OF TABLES

ADDENDUM 3: LIST OF FIGURES

ADDENDUM 4: DUTCH COCHRANE CENTER CHECKLIST FOR THE QUALITY ASSESSMENT OF RANDOMISED CONTROLLED TRIALS

FORMULIER II

voor het beoordelen van een

RANDOMISED CONTROLLED TRIAL (RCT)

Evidence-Based RichtlijnOntwikkeling

Formulier II: beoordeling randomised controlled trial (RCT)

Dit formulier is bestemd voor het beoordelen van randomised controlled trials (RCT's). RCT's worden uitgevoerd ter bepaling van het effect van een therapeutische of preventieve interventie. Soms wordt het effect van een diagnostische interventie ook door middel van een RCT onderzocht.

Dit formulier is ontwikkeld door een werkgroep bestaande uit vertegenwoordigers van het Dutch Cochrane Centre, het Kwaliteitsinstituut voor de Gezondheidszorg CBO, het Nederlands Huisartsen Genootschap, het institute for Medical Technology Assessment, de Werkgroep Onderzoek Kwaliteit, het College voor Zorgverzekeringen, Zorgonderzoek Nederland (ZonMw) en de Orde van Medisch Specialisten en wordt ondersteund door het Nederlands Paramedisch Instituut, de Vereniging voor Integrale Kankercentra en de Werkgroep Infectieziektenpreventie.

Voor het beoordelen van de kwaliteit van andere typen onderzoek zijn eveneens formulieren ontwikkeld. Deze staan samengevat in onderstaande tabel.

Type onderzoek	Formulier
Dwarsdoorsnedeonderzoek (waarde diagnostische test)	I
Randomised controlled trial (RCT)	II
Cohortonderzoek	III
Patiënt-controleonderzoek	IV
Systematische review van	
RCT's (therapie en preventie)	Va
diagnostisch onderzoek	Vb
observationeel onderzoek (etiologie/"harm"/prognose)	Vc
Economische evaluatie	VI
Richtlijn	AGREE

Instructie beoordeling

- De bruikbaarheid van een publicatie voor een richtlijn wordt in de formulieren op drie facetten beoordeeld: validiteit, toepasbaarheid in de praktijk en toepasbaarheid in de Nederlandse gezondheidszorg
- Daarnaast wordt gevraagd om de belangrijkste kwantitatieve gegevens te extraheren en op een uniforme wijze te presenteren.
- De opmaak van de beoordelingsformulieren maakt het u makkelijk:

a) op diverse plaatsen is een beslismoment ingebouwd: indien een publicatie op dat moment niet aan de vereisten van validiteit of toepasbaarheid voldoet hoeft u met de beoordeling niet verder te gaan.
b) de criteria en manier van data-extractie worden telkens op de tegenoverliggende pagina kort toegelicht.

Zend opmerkingen of suggesties aangaande dit formulier naar cochrane@amc.uva.nl.

Vraag 1. *Randomisatie*. Randomisatie is een methode waarbij gebruikgemaakt wordt van het toeval om de te onderzoeken interventie en de controlebehandeling(en) toe te wijzen aan de patiënt. Randomisatie houdt in dat ieder individu (of andere eenheid van randomisatie) een gelijke kans heeft om elk van de interventies te krijgen. Een goede randomisatie kan bijvoorbeeld gebruikmaken van een tabel met aselecte (random) getallen of van een door een computer aangemaakte randomisatielijst.
Er dient gewaarschuwd te worden voor andere methoden van allocatie die soms wel als randomisatie beschreven zijn, maar dit niet echt zijn: allocatie op geboortedatum, volgorde van binnenkomst, dag van de week, maand van het jaar, dossiernummer. Deze methoden heten wel “quasi random”. In dat geval is het belangrijk om extra aandacht te geven aan de vergelijkbaarheid van de groepen (vraag 6).

Vraag 2. *Blindering van de randomisatie*. Procedure waarbij wordt voorkomen dat degene die de patiënt beoordeelt en insluit op de hoogte kan zijn van de randomisatievolgorde. Goede manieren zijn: gebruik van centrale randomisatieschema’s; randomisatieschema’s die door een trial-apotheek worden beheerd; genummerde en gecodeerde verpakkingen met identieke placebo- en verum-medicatie (= werkzame medicatie); genummerde, niet-doorzichtige enveloppen; een op locatie aanwezige computer waarvan de randomisatievolgorde pas wordt vrijgegeven na opgave van de patiëntenkarakteristieken.
De in de toelichting bij vraag 1 genoemde “quasi random” procedures zijn per definitie niet blind voor randomisatie omdat degene die de patiënt in het onderzoek insluit, kan voorzien welke behandeling de patiënt zal krijgen.
Blindering van randomisatie *(concealment of allocation)* dient te worden onderscheiden van blindering van patiënten, behandelaars en effectbeoordelaars.

Vraag 3. *Blindering patiënten*. Door blindering van de patiënt wordt voorkomen dat: a) deze bewust of onbewust een grotere compliance met het protocol zal hebben, b) de uitkomstmeting door voorkeuren voor behandeling wordt beïnvloed. Blindering van de patiënt wordt bereikt door de verumbehandeling (= werkzame behandeling) en placebobehandeling identiek te maken. Medicatie moet dezelfde kleur, grootte, smaak en consistentie hebben. Ook niet-medicamenteuze placebo-interventies, zoals bijvoorbeeld fysiotherapie of ruggordels, dienen voldoende identiek te zijn om geloofwaardig over te komen. Evaluatie van het succes van blindering is gewenst, maar is voor dit item niet noodzakelijk. Indien een onderzoek als dubbelblind wordt beschreven dient u goed na te gaan om wie het gaat: patiënt, behandelaar en/of effectbeoordelaar. Dit is op voorhand niet altijd duidelijk.

Vraag 4. *Blindering behandelaars*. Door blindering van de behandelaar wordt voorkomen dat deze, omdat hij op de hoogte is van de aard van de toegewezen behandeling: a) een bepaald enthousiasme zal uitstralen (selectieve vergroting van het placebo-effect), b) verschillende mate van adherentie aan het onderzoeksprotocol zal hebben (door bijvoorbeeld aan de placebogroep aanvullende behandeling aan te bieden). Evaluatie van het succes van blindering is gewenst, maar is voor dit item niet noodzakelijk.
Indien een onderzoek als dubbelblind wordt beschreven dient u goed na te gaan om wie het gaat: patiënt, behandelaar en/of effectbeoordelaar. Dit is op voorhand niet altijd duidelijk.

Vraag 5. *Blindering effectbeoordelaars.* Door blindering van de effectbeoordelaar wordt voorkomen dat deze de effecten van interventie en controlebehandeling verschillend zal beoordelen. Evaluatie van het succes van blindering is gewenst, maar is voor dit item niet noodzakelijk.
Indien een onderzoek als dubbelblind wordt beschreven dient u goed na te gaan om wie het gaat: patiënt, behandelaar en/of effectbeoordelaar. Dit is op voorhand niet altijd duidelijk.

Beoordeling van de kwaliteit van een randomised clinical trial (RCT)

Naam beoordelaar:.....Datum:.....
Titel:.....
Auteurs:.....
Bron: .....

Beoordeling van de validiteit

Korte beschrijving van de interventie: .....
.....
Korte beschrijving van de controlebehandeling(en): .....
.....

VALIDITEIT

1. Was de toewijzing van de interventie aan de patiënten gerandomiseerd?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

2. Degene die patiënten in het onderzoek insluit hoort niet op de hoogte te zijn van de randomisatievolgorde. Was dat hier het geval?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

3. Waren de patiënten geblindeerd voor de behandeling?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

4. Waren de behandelaars geblindeerd voor de behandeling?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

5. Waren de effectbeoordelaars geblindeerd voor de behandeling?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

Vraag 6. *Vergelijkbaarheid groepen.* De groepen moeten aan het begin van het onderzoek op belangrijke prognostische kenmerken voldoende gelijk zijn. Theoretisch zou alleen de toegewezen behandeling tussen de groepen verschillend moeten zijn.
Bij beoordeling kan worden gelet op:
a) Belangrijke prognostische variabelen, waaronder bijvoorbeeld ziekteduur, ernst, co-medicatie, co-morbiditeit
b) Uitgangswaarden van de belangrijkste uitkomstmaten c)
Demografische gegevens (geslacht, leeftijd)
Kleine verschillen kunnen op basis van toeval optreden. Bij grote verschillen dient beredeneerd te worden in welke mate en in welke richting de resultaten beïnvloed kunnen worden.
Er kan door de onderzoekers ook door middel van multivariate analyses gecorrigeerd zijn voor verschillen in prognostische factoren tussen de groepen.

NB: Als sprake is van *quasi randomisation* (zie vraag 1), is het belangrijk om extra aandacht te geven aan de vergelijkbaarheid van de groepen.

Vraag 7. *Loss-to-follow-up.* Het is belangrijk om per groep de aantallen patiënten bij randomisatie en bij follow-up te vergelijken. Relatief grote uitval (loss-to-follow-up) maakt een onderzoek gevoelig voor selectieve loss-to-follow-up. Aantallen en redenen voor uitval dienen gerapporteerd te zijn. Ook als er geen uitvallers waren dient dit te zijn beschreven.
Indien de redenen van uitval uit het onderzoek of de absolute aantallen uitvallers tussen de groepen verschillend zijn en tot een vertekening van de uitkomsten kunnen leiden, heet dit selectieve loss-to-follow-up.
Het is niet mogelijk om op voorhand per indicatiegebied aan te geven welk percentage loss-to-follow- up nog acceptabel is.

Vraag 8. *Intention-to-treat analyse.* Bij de analyse dient de allocatie door randomisatie gerespecteerd te worden. De patiënt hoort bij de oorspronkelijk door randomisatie gevormde groep, ongeacht eventuele co-interventies, non-compliance en dergelijke (zie vraag 9).
Naast intention-to-treat analyse kan ook nog een per-protocol analyse worden gepresenteerd. Hierbij worden alleen gegevens van patiënten gebruikt die volgens het onderzoeksprotocol zijn behandeld. Bedenk, dat een per-protocolanalyse zeer misleidend kan zijn.

Vraag 9. *Vergelijkbaarheid behandeling.* De behandeling van de patiënten in de verschillende groepen dient behalve het door randomisatie beoogde contrast geen verschillen te vertonen. Bij goed geblindeerde behandelingen is de vergelijkbaarheid van behandelingen in de regel geen probleem.
Bij de beoordeling kan worden gelet op:
a) Co-interventies. Verdeling van behandelingen anders dan de door randomisatie toegewezen. Soms worden deze door de onderzoekers onder controle en dus gelijk gehouden. In andere gevallen worden de co-interventies per groep gerapporteerd. Indien er geen melding van co-interventies wordt gemaakt dient men op de hoede te zijn.
b) Contaminatie. In geval van contaminatie krijgt of zoekt de patiënt in de loop van het onderzoek precies de behandeling die eigenlijk aan de andere groep toegewezen is.
c) Compliance. Indien de compliance met de toegewezen behandeling in de ene groep veel groter is dan in de andere kan dit de interpretatie van de gegevens verstoren.

Vraag 10. *Algemeen oordeel*. Hier wordt een inschatting van de validiteit en toepasbaarheid gevraagd. Let hierbij ook op eventuele fouten in het onderzoek die funest zijn voor de validiteit ervan (*red flags, fatal flaws*). Er zijn geen regels te geven voor welke items positief gescoord moeten worden of welk aantal items tenminste positief gescoord moeten worden. Dit is deels afhankelijk van de “state-of-the- art” met betrekking tot het betreffende onderwerp. Het gaat er hier om het samenvattend oordeel van wat de beoordelaar de werkgroep zou willen mededelen over de bruikbaarheid van het artikel voor de besluitvorming.

6. Waren de groepen aan het begin van de trial vergelijkbaar?
[ ] Ja
[ ] Nee, maar in de analyses is hiervoor wel gecorrigeerd
[ ] Nee, en in de analyses is hiervoor niet gecorrigeerd
[ ] Te weinig informatie in het artikel om dit te beantwoorden

7. Is van een voldoende proportie van alle ingesloten patiënten een volledige follow-up beschikbaar?
[ ] Ja
[ ] Nee ⇐ Is selectieve loss-to-follow-up voldoende uitgesloten?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden / loss-to-follow-up niet beschreven

8. Zijn alle ingesloten patiënten geanalyseerd in de groep waarin ze waren gerandomiseerd?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

9. Zijn de groepen, afgezien van de interventie, gelijk behandeld?
[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

TUSSENOORDEEL

10. Zijn de resultaten van het onderzoek valide en toepasbaar?

[ ] Voldoende valide en toepasbaar	⇐ ga verder bij 11
[ ] Twijfelachtig	⇐ ga verder bij 11
[ ] Onvoldoende valide en toepasbaar	U kunt stoppen met het invullen van de checklist, tenzij er geen betere artikelen op dit gebied zijn (terugkoppelen naar de werkgroep)

Vraag 11. *Resultaten*

Keuze uitkomst en follow-up duur. Auteurs zijn soms geneigd de meest in het oog springende (significante) resultaten als belangrijkste te presenteren. Het is als beoordelaar belangrijk om vooraf een indruk te vormen van de klinisch of beleidsmatig meest relevante uitkomst(en) en follow- upmoment. Dit zijn de belangrijkste parameters die meegenomen dienen te worden in de rapportage naar de groep. Pas ervoor op niet slechts op de hiërarchie van de auteurs van het artikel af te gaan.

Dichotome uitkomsten. In geval van dichotome uitkomsten (uitkomsten die slechts 2 waarden kunnen aannemen, bijvoorbeeld wel of niet genezen) kunnen verschillende associatiematen berekend worden: relatieve risico, relatieve risicoreductie, absolute risicoreductie en number needed to treat. Als de oorspronkelijke getallen gepresenteerd worden (voor notatie: zie Tabel), kan men deze associatie-maten zelf berekenen. Is dit niet het geval, dan moet men volstaan met het overnemen van de door de auteurs gepresenteerde associatiemaat (inclusief het 95%-betrouwbaarheidsinterval). Dit moet u ook doen, indien de auteurs een multivariate statistische analyse hebben uitgevoerd ter correctie voor verschillen in prognostische factoren tussen de groepen.
De formules voor het zelf berekenen van een 95%-betrouwbaarheidsinterval staan in de appendix. (Zie ook de verschillende rekenmachientjes op internet, bijv. op http://minerva.minervation.com/cebm/ of http://www.cebm.utoronto.ca/practise/ca/statscal/.)

Formules voor het berekenen van verschillende associatiematen in een RCT	Uitkomst * aanwezig	afwezig	Totaal
Interventiegroep	a	b	a + b
Controlegroep	c	d	c + d
Kans op gebeurtenis (risico) in de interventiegroep	a / (a + b)		
Kans op gebeurtenis (risico) in de controlegroep	c / (c + d)		
Absolute risico reductie (ARR)	a/(a + b) – c/(c + d)		
Number needed to treat (NNT)	1/ ARR = 1 / [| a/(a + b) – c/(c + d) |]		
Relatieve risico (RR)	[a/(a + b)] / [c/(c + d)]		
Relatieve risico reductie (RRR):			
- in geval van een ongunstige uitkomst	1 – RR		
- in geval van een gunstige uitkomst	RR – 1		

* *De uitkomst (of het eindpunt) kan zowel gewenst (bijvoorbeeld genezing) als ongewenst zijn (bijvoorbeeld bijwerking van een medicijn, overleden).*

Absolute risico reductie (ARR) = risicoverschil = verschil in absolute risico op de uitkomst tussen de interventie- en controlegroep. Indien de bestudeerde uitkomst (eindpunt) een gunstige is (genezen), wordt ook wel gesproken van een *absolute benefit increase (ABI).*
Number needed to treat (NNT) = aantal patiënten dat met de interventie behandeld dient te worden om één ongewenste gebeurtenis minder of één gewenste gebeurtenis meer te bereiken dan met de controlebehandeling verkregen zou zijn.
Relatieve risico (RR) = verhouding van absolute risico op de uitkomst tussen interventie- en controlegroep. Indien de bestudeerde uitkomst (eindpunt) een gunstige is (genezen), wordt ook wel gesproken van een *benefit ratio (BR).*
Relatieve risico reductie (RRR) = relatieve risicoverschil. In geval van een ongunstige uitkomst (bijv. overleden) en een gunstig effect van de onderzochte interventie (RR < 1 en ARR < 0) is RRR de proportionele verlaging van het risico op de slechte uitkomst (dan: RRR = 1 – RR). Bij een gunstige uitkomst (bijv. genezen) en een gunstig effect van de onderzochte interventie (RR > 1 en ARR > 0) spreekt men van “relative benefit increase” (RBI). RBI is de proportionele verhoging van het “risico” (kans) op de gunstige uitkomst (dan: RBI = RR – 1).

Continue uitkomsten. Bij continue uitkomsten wordt per behandelarm het gemiddelde effect berekend. De hier van toepassing zijnde associatiemaat is het verschil van beide gemiddelden. Voor het berekenen van een 95%-betrouwbaarheidsinterval zijn ook nog – per behandelarm – de standaard- deviatie (SD) en het aantal patiënten nodig (N). NB: Let er bij de dataextractie voor op dat de standaarddeviatie [SD] iets anders is dan de standard error (of the mean) [SE(M)]! De standaard- deviatie is de standard error of the mean maal de wortel uit het aantal patiënten in de groep. In formule: SD = SEM * √N.

11. Resultaten
In de onderstaande tabellen kunt u de meest relevante resultaten weergeven. Niet alle parameters zullen echter in het artikel vermeld staan. Deze zijn echter vaak zelf uit te rekenen met de gegevens uit het artikel (zie toelichting).

DICHOTOME UITKOMSTEN (genezen / niet-genezen; in leven / overleden)

Uitkomst: .....
Follow-up: ..... weken / maanden / jaar

Groep	Uitkomst aanwezig	afwezig	Totaal
Interventiegroep			
Controlegroep			

Kans op gebeurtenis in de interventiegroep	
Kans op gebeurtenis in de controlegroep	
Absolute risico reductie (ARR)	
Number needed to treat (NNT)	
Relatieve risico (RR)	
Relatieve risico reductie (RRR)	

CONTINUE UITKOMSTEN (bijvoorbeeld bloeddruk, pijnscore, kwaliteit-van-leven score)

Uitkomst: .....
Follow-up: ..... weken / maanden / jaar

Groep	Gemiddelde	SD	Aantal (N)
Interventiegroep			
Controlegroep			
Verschil van gemiddelden + 95%-BI			

Vraag 12 en 13. *Toepasbaarheid in de Nederlandse gezondheidszorg.* Beide vragen zijn een belangrijk onderdeel van richtlijnontwikkeling en dienen daarom in de werkgroep bediscussieerd te worden.

Vraag 14. *Conclusie met betrekking tot het artikel en de waarde van de interventie*
Geef hier een globale samenvatting van het eindoordeel over het artikel. Probeer, indien aanwijzingen bestaan voor vertekening van de resultaten, tenminste een inschatting te maken van de richting van de vertekening (overschatting of onderschatting van het effect van de interventie) en zo mogelijk ook over de grootte van de vertekening. Eventuele aanwijzingen voor mogelijke belangenverstrengeling van de auteurs met belanghebbende opdrachtgevers, kunt u hier ook rapporteren. Ook is het verstandig ingezonden brieven en/of redactionele commentaren op het hier door u beoordeelde onderzoek te raadplegen bij het formuleren van uw conclusie.

Voorbeeld: “Eindoordeel voldoende. Goed opgezet artikel. Door de aard van de interventie (oefentherapie bij lage rugpijn) is blindering van de behandelaar en patiënt vrijwel onmogelijk. Door te vergelijken met een gespreksgroep wordt echter wel goed gecorrigeerd voor aandachtseffecten. Oefentherapie lijkt effectief bij subacute en chronische lage rugpijn”.

TOEPASBAARHEID IN DE NEDERLANDSE GEZONDHEIDSZORG

12. Kan het gevonden resultaat worden toegepast op de Nederlandse situatie?
(hierbij valt bijvoorbeeld te denken aan de beschikbare therapeutische faciliteiten)

[ ] Ja
[ ] Nee
[ ] Te weinig informatie in het artikel om dit te beantwoorden

13. Op welk(e) echelon(s) kan het resultaat worden toegepast?
(meerdere opties tegelijk mogelijk)

[ ] algemene bevolking
[ ] eerste lijn
[ ] tweede lijn
[ ] academische ziekenhuizen
[ ] perifere ziekenhuizen
[ ] derde lijn

CONCLUSIE

14. Conclusie met betrekking tot het artikel en de waarde van de interventie

APPENDIX:

Formules voor het zelf berekenen van een 95%-betrouwbaarheidsinterval (95%-BI)

DICHOTOME UITKOMSTEN:

NB : op diverse internetsites zijn voor deze berekeningen ook rekenmachientjes beschikbaar bijvoorbeeld op http://minerva.minervation.com/cebm/ of
http://www.cebm.utoronto.ca/practise/ca/statscal/

Absolute risicoreductie (ARR):

$SE[ARR] = \sqrt{[\ ab / (a+b)^3 + cd / (c+d)^3\ ]}$

95%-BI voor ARR: $ARR \pm 1{,}96 * SE[ARR]$

Relatieve Risico (RR) (via natuurlijke log-transformatie):
$SE[LN(RR)] = \sqrt{[\ 1/a - 1/(a+b) + 1/c - 1/(c+d)\ ]}$

95%-BI voor RR: $e^{LN(RR) \pm 1{,}96 * SE[LN(RR)]}$

CONTINUE UITKOMSTEN:

Verschil van gemiddelden:

$$SD_P = \sqrt{[\ (N_I - 1) * SD^2_I + (N_C - 1) * SD^2_C\ ) / (\ N_I + N_C - 2\ )\ ]}$$

95%-BI voor verschil van gemiddelden:

$$\text{Gemiddelde}_I - \text{Gemiddelde}_C \pm t_{0,975} * SD_P * \sqrt{[\ 1/N_I + 1/N_C\ ]}$$

I = Interventiegroep; C = Controlegroep; $t_{0,975}$ = benodigde waarde van t-verdeling met (N_I+N_C-2) vrijheidsgraden (opzoeken in tabel van t-verdelingen)

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